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THE NONPROTEIN NITROGEN OF THE BLOOD IN ATROPHIC INFANTS *

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The purpose of our work was the determination of the nonprotein nitrogen of the blood of infants, particularly of infants suffering from disorders of nutrition of the severer types. The blood was taken in quantities of 3 to 5 c.c. from the longitudinal sinus, following the directions of Helmholz.[1] The poor condition of most of our atrophic infants was the reason for taking as small quantities of blood as possible. In most of the cases the total nonprotein nitrogen and the urea nitrogen were determined, the former according to the method of Folin and Denis,[2] the latter by the Van Slyke and Cullen[3] modification of Marshall's[4] method. The portion of the alcoholic filtrate of the blood which is used for the determination of the urea nitrogen must be taken before the addition of zinc chlorid, because this substance interferes with the urease action. Creatin and creatinin were determined in a few of our normal and pathologic cases according to the method of Folin[5] as modified by Myers and Fine.[6] We found 1.1 to 1.6 mg. creatinin nitrogen and 3.0 to 7.6 mg. creatin nitrogen per 100 c.c. of blood, these figures agreeing well with those found in the table of Veeder and Johnston,[7] but subject to the criticism of Hunter and Campbell,[8] as our picric acid solution was old and not protected from light. In a few cases the amino-acid nitrogen was determined according to Van Slyke.[9] In four cases of our normal series and in five of the atrophic infants we found 3.5 to 7 mg. nitrogen per 100 c.c. of blood, figures agreeing with those obtained by Pettibone and Schlutz.[10]

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* From the Otho S. A. Sprague Institute Laboratory of the Children's Memorial Hospital.

1. Helmholz, H. F.: Am. Jour. Dis. Child., 1915, **10,** 194.
2. Folin and Denis: Jour. Biol. Chem., 1912, **11,** 527.
3. Van Slyke and Cullen: Jour. Am. Med. Assn., 1914, **62,** 1558.
4. Marshall: Jour. Biol. Chem., 1914, **17,** 351.
5. Folin: Jour. Biol. Chem., 1914, **17,** 475.
6. Myers and Fine: Chem. Composit. of the Blood, etc.
7. Veeder and Johnston: Am. Jour. Dis. Child., 1916, **12,** 136.
8. Hunter and Campbell: Jour. Biol. Chem., 1916, **28,** 335.
9. Van Slyke: Jour. Biol. Chem., 1915, **13,** 407.
10. Pettibone and Schlutz: Jour. Am. Med. Assn., 1916, **67,** 262.

Table 1 gives the results of total nonprotein and urea nitrogen determinations in mg. per 100 c.c. of blood. The sixteen infants, so-called feeding cases, were all doing well. The determinations were made before feedings, the infants being fed on mixtures of cow's milk at four-hour intervals. In most cases duplicate determinations were made, at least of the total nonprotein nitrogen, the duplicates agreeing rather well in most instances (cf. table). In Cases 6, 13 and 15 the difference exceeds 2 mg. It was not always possible to make duplicates of the urea nitrogen determinations, but where made, the agreement was quite good.

TABLE 1.—CONVALESCENT FEEDING CASES

No.	Name	Date	Age, Mos.	Wt., Lbs.	Mg. Total Nonprotein Nitrogen per 100 C.c. Blood		Mg. Urea N per 100 C.c. Blood	Remarks
1	Nel. O.	12/28/15	1	5.2	22.0	....	7.4	Discharged improved, 1/18/16
2	Tom. J.	3/ 3/16	2	7.0	23.6	23.6	11.5	
3	Florence Z.	2/18/16	3	9.10	26.2	26.0	....	Before a meal
	Florence Z.	.....	...	.....	27.9	27.5	....	After a meal
4	Tom. J.	4/10/16	3	8.6	23.0	23.0	12.1	Discharged; doing well
5	Kline F.	2/26/16	3	5.4	22.0	21.3	13.0	Premature; doing well
6	John K.	4/15/16	3	6.4	25.7	23.0	11.0	Discharged; doing well
7	Vernon G.	6/ 3/16	4½	7.13	24.8	24.5	13.5	Improved; doing well
8	James B.	12/21/15	5	8.6	23.0	22.4	....	Discharged; doing well
9	Elmer D.	3/18/16	5	11.3	25.9	25.2	13.1	Doing well
10	Bridget L.	12/18/15	6	10.2	23.4	21.8	14.4	Discharged; doing well
11	Magdalene G.	3/14/16	6	6.4	27.0	26.0	12.6	Discharged; doing well
12	Leon T.	4/20/16	6	10.8	24.3	....	....	Discharged; going well
	Leon T.	6/ 5/16	8	11	21.6	20.2	10.2	Discharged; doing well
13	Jos. N.	4/14/16	8	11.13	26.8	24.6	13.6	Discharged; doing well
14	Amelia P.	6/22/16	8	10.9	24.0	....	12.1	Discharged; doing well
15	Helen S.	6/13/16	10	10.10	24.0	21.4	8.8	Discharged; doing well
16	Malvina G.	2/24/16	16	12.8	20.0	18.2	11.0	Before a meal
	Malvina G.	.....	...	.....	27.3	26.3	12.0	After a meal

There is no uniformity of opinion in regard to the normal limits of the total nonprotein nitrogen of the blood in adults. Folin and Denis give 22 to 26 mg. per 100 c.c. of blood as the normal. Folin, Denis and Seymour,[11] Tileston and Comfort,[12] Frothingham and Smillie,[13] Rown-

11. Folin, Denis and Seymour: Arch. Int. Med., 1914, **13,** 224.
12. Tileston and Comfort: AM. JOUR. DIS. CHILD., 1915, **10,** 278; ibid., Arch. Int. Med., 1914, **14,** 620.
13. Frothingham and Smillie: Arch. Int. Med., 1914, **14,** 541.

tree, Marshall and Baetjer,[14] and others accept as normal values those given by Folin and Denis,[2] or values varying between 20 and 30 mg. Others, as, for instance, McLean and Selling,[15] say the normal varies from 23 to 36 mg. Of greater interest to us here are the determinations in younger individuals. Schlutz and Pettibone[16] found in 9 infants from ½ hour to 10 days of age, 23 to 40 mg.; Veeder and Johnston, working on normal children from 2 to 14 years of age, get 22 to 33 mg. (5 exceeding 30 mg.); Leopold and Bernhard[17] get 19 to 40 mg. in 50 patients free from renal involvement, but suffering from various other diseases; the ages varied from 2 to 13 years; in 21 cases the total nonprotein nitrogen exceeded 30 mg. All these investigators used the method of Folin and Denis. Greenwald[18] objects to the use of alcohol in the precipitation of the blood, because the precipitate carries with it amino-acids and does not precipitate some lipoid nitrogen. In his determinations on 6 normal individuals, by the method of Folin and Denis and by his modification, he invariably finds higher values for the total nonprotein nitrogen by his method. In two instances his values exceed 30 mg. (31.0 and 31.7 mg.). Gettler and Baker[19] use hydrochloric acid and mercuric chlorid for the precipitation of the proteins. In their 30 patients, ranging from 17 to 60 years of age, they get from 27 to 52 mg. per 100 c.c. of blood, according to their table. Bang,[20] using his own method, not given in his paper, in 42 individuals got from 19 to 39 mg. The age of the individuals varied from new-born to 82 years. Although he gives 25 mg. as the average value, he got values greater than 30 mg. in 9 cases.

As Gettler and Baker[19] remark, the values for normal individuals given in the literature disagree more or less, and this may be due to the different methods used by the various workers, to the nature of the food or the time after a meal that the blood is taken. But quite aside from these factors is another very important one, namely, the latitude of the term "normal" individual. On the basis of our results we have been naturally very much inclined to accept as normal for the total nonprotein nitrogen of infants' blood, 22 to 30 mg. when determined by the Folin and Denis method. While our babies were doing well on nontherapeutic foods, they were convalescent from disorders of nutrition, and were, with few exceptions, decidedly underweight. *Sensu strictiori,* they are not normal, nor are many of the so-called normal

14. Rowntree, Marshall, Baetjer: Arch. Int. Med., 1915, **15,** 543.
15. McLean and Selling: Jour. Biol. Chem., 1914, **19,** 31.
16. Schlutz and Pettibone: Am. Jour. Dis. Child., 1915, **10,** 206.
17. Leopold and Bernhard: Am. Jour. Dis. Child., 1916, **11,** 432.
18. Greenwald: Jour. Biol. Chem., 1915, **21,** 61.
19. Gettler and Baker: Jour. Biol. Chem., 1916, **25,** 211.
20. Bang: Biochem. Ztschr., 1915, **72,** 104 and 119.

cases of other investigators, not even some of those of Gettler and Baker. It is not at all impossible that a somewhat more guarded selection of individuals may aid in doing away with the greater discrepancies.

In two of our cases (3 and 6) the determinations of the nonprotein nitrogen were repeated after feeding, Case 3 perhaps showing a slight, Case 6 a definite, increase similar to the cases of Tileston and Comfort,[12] who found an increase after a heavy meal of meat. Bang's[20] work on animals and man shows similar results.

Table 2 contains the results we obtained in atrophic infants arranged according to the amount of nonprotein nitrogen found. All these cases belong to a severe type of decomposition. With the exception of Cases 2 and 9, the urine did not show any of the ordinary pathologic changes; the urine of these two children contained pus. Of the 26 cases, 15 had more than 30 mg. nonprotein nitrogen per 100 c.c. of blood, and 11 had less than 30 mg. Of the 15 patients with more than 30 mg., 12 died and the other 3 did poorly when they left the hospital. Of the 11 cases of atrophy with less than 30 mg. nonprotein nitrogen, 3 patients died, 6 did fairly well or well, and 2 poorly. In our series of observations it is certainly a striking feature that of the 15 patients who died, 12 had a nonprotein nitrogen over 30 mg. and of these, 9 over 35 mg., while 3 fatal issues fell to the share of the group with less than 30 mg. nonprotein nitrogen. The occurrence of a relatively high nonprotein nitrogen in our cases may be the result of the interplay of a variety of factors, such as retention or overproduction in relation to the water economy of the organism. For instance, Bang,[20] in his animal experiments, has shown that starvation leads to a very marked increase in the nonprotein nitrogen, and particularly of the urea nitrogen, provided no water is given. Veeder and Johnston report one case of starvation with a rather scant increase of the nonprotein nitrogen (31 to 35 mg.). Bang mentions a loss of water by the blood in cases of starvation. We have not sufficient data to enter into a detailed discussion of the possible explanations of the relatively high nonprotein nitrogen in our cases. Only in a few cases did we determine the number of red cells and hemoglobin in order to detect a possible marked concentration of the blood. Such determinations were made on Cases 4, 7, 17, 23 and 24 — the first two having a relatively high nonprotein nitrogen, the last two a relatively low nonprotein nitrogen. In no case was the red count above 4,000,000 and the hemoglobin was always low. Aside from these determinations, the similarity of the cases with high or low nonprotein nitrogen does not speak in favor of a concentration of the blood as a factor in the production of the high nonprotein nitrogen, although the final decision must be left to a special investigation of this point. The possible influence of substances summarized in the total nonprotein nitrogen on the course of the disease will have to be considered in the future.

TABLE 2.—ATROPHIC INFANTS

No.	Name	Date, 1916	Age, mos.	Wt., Lbs.	Wt. Curve	Lect. T.	Mg. Total Nonprotein Nitrogen per 100 C.c. Blood		Mg. Urea N per 100 C.c. Blood	Remarks
1	Harold Ne.	3/17	2	5.8	S*	96.5	58.4	58.0	34.3	Died 4/6/16
2	Louise K.	4/16	9	10.2	L	99.0	52.4	52.0	29.5	Pus in urine; died 4/23
3	Regina M.	5/15	3	6.3	S	97.0	51.6	48.8	37.0	Died 6/17
4	Mazie M.	1/15	1	4.3	L	98.0	43.0	....	20.2	Died 2/7
5	Rosie C.	5/29	5	7.14	G	97.0	38.6	37.0	23.0	Died 7/17
6	Tom Mc.	4/12	3	6.7	L	96.0	38.0	37.3	21.8	Died 5/23
7	Esther W.	3/10	2½	6.3	G	97.0	37.4	36.0	16.0	Died 3/27
8	Louise H.	4/ 8	10	6.13	S	96.0	37.0	37.0	21.5	Died 4/16
9	John P.	4/17	4	7.4	S	100.0	36.0	....	15.5	
	John P.	5/10	5	7.2	S	98.0	31.7	....	15.0	Pus in urine; improved, 6/17
10	Mollie F.	2/25	7	6.10	L	97.0	35.3	34.7	17.6	
	Mollie F.	7/18	12	6.12	L	98.0	38.8	....	20.3	Died 7/18
11	Rose P.	7/17	5	8.2	G	97.0	34.8	33.0	20.0	Doing poorly 7/30
12	Beverley G.	2/12	4	5.3	S	96.0	34.0	29.4	12.7	Died 3/1
13	Richard S.	3/15	2	5.12	S	97.0	33.3	32.8	10.0	
	Richard S.	5/18	4	5.12	S	98.0	29.7	....	10.4	Doing poorly 7/5
14	Fred W.	1/31	3	6.10	L	97.0	32.4	....	15.9	Died 2/19
15	Walker W.	1/24	8	7.12	L	97.0	30.7	....	....	Died 1/30
16	Myrtle D.	6/ 2	7	6.12	L	97.0	29.7	29.0	10.0	Died 6/19
17	John S.	5/13	8	7.12	S	100.0	29.0	24.9	8.0	
	John S.	5/27	8½	8.4	G	98.0	26.7	....	10.8	Doing fairly well 6/8
18	Harold Na.	4/19	8	7.9	L	96.0	26.9	26.4	12.3	Died 4/23
19	Ray S.	12/30	6	7.12	L	97.0	25.2	24.8	12.0	Died 1/8
20	Alice T.	6/28	8	9.0	S	98.0	24.8	22.6	10.8	Doing fairly well 7/14
21	Helen M.	7/12	2½	5.6	S	98.0	24.3	22.8	13.6	Doing poorly 7/30
22	Harry B.	4/26	6	6.10	G	97.0	23.1	....	8.9	Doing well 7/15 (9 pounds)
23	Robert S.	3/10	2½	6.0	S	98.0	23.0	20.6	6.1	
	Robert S.	4/29	4	7.8	S	98.0	19.5	19.3	5.6	
	Robert S.	5/ 3	...	7.8	S	100.0	21.2	....	7.7	Doing well 6/20
24	Helen S.	5/ 1	5	5.4	S	99.0	22.6	....	7.6	Doing poorly
25	Nellie O.	12/28	1	5.2	S	96.0	22.0	....	7.4	
25	Nellie O.	4/23	5	5.3	S	96.0	25.0	....	7.7	Doing fairly well 7/1
26	Louise K.	7/11	3	5	G	97.0	21.5	21.3	7.3	Doing well 7/28

* S = weight curve stationary when blood was taken; L = losing weight; G = gaining weight.

With reference to the relationship of the urea nitrogen to the total nonprotein nitrogen, Table 3 gives a survey of our series of cases. A is calculated from Table 1, leaving the figures obtained after feeding out of consideration. B is calculated from those cases of Table 2, wherein the nonprotein nitrogen exceeds 30 mg., and B2 from the remainder of Table 2, using in Cases 23 and 25 the averages for the calculation.

TABLE 3.—SUMMARY OF AUTHORS' CASES

	Nonprotein N	Urea N	Nonprotein N Minus Urea N
A (16 cases)	24	12	12
B (15 cases)	39	20	19
B2 (11 cases)	25	10	15

It is a rather precarious undertaking to utilize averages from a relatively small number of cases which show quite extensive variations. We will, therefore, not dilate on the possible significance of these figures any further than to point out that the burden of the increase of the nonprotein nitrogen does not seem to be borne preponderantly by the urea nitrogen.

Another circumstance may be of significance: Where a relatively low nonprotein nitrogen was associated with an urea nitrogen markedly below 50 per cent. of the nonprotein nitrogen, the infants were, on the whole, getting on rather well (of Cases 17, 22, 23, 24, 25 and 26, only Case 24 did poorly). If such an occurrence should prove to be a concomitant feature of certain phases of the reparation from disorders of nutrition, it could easily explain the low urea nitrogen of Cases 1 and 15 of Table 1.

TABLE 4.—ALIMENTARY INTOXICATION

No.	Name	Date	Age, Mos.	Wt., Lbs.	Mg. Total Nonprotein Nitrogen per 100 C.c. Blood		Mg. Urea N per 100 C.c. Blood	Remarks
1	John O.	2/12/16	13	21.0	67.6	....	31.7	Died 2/13; Temp. 106
2	Eugene A.	3/17/16	5	14.10	60.0	57.5	48.3	Died 3/18; edema
3	E. Smith	2/20/16	7	15.4	25.6	....	11.0	Feeding case; discharged well, 3/2/16
	E. Smith	4/ 5/16	8½	11.0	53.0	....	37.2	Died 4/7
4	John J.	4/21/16	4	9.9	29.4	....	16.1	Died 4/24
5	Leon C.	7/13/16	12½	17.2	28.0	27.2	18.4	Died 7/19
6	Loren H.	2/27/16	9	13.14	26.7	26.4	17.3	Died 3/1

Table 4 contains the results obtained in some cases of alimentary intoxication.

The urines of all the patients contained albumin and casts, so that in the cases with high nonprotein nitrogen (Cases 2 and 3) a renal insufficiency may play its rôle. Case 3 is of interest. When the infant was in the hospital the first time, suffering with a mild disturbance of nutrition, its nonprotein nitrogen and urea nitrogen were about normal. Six weeks after its discharge it returned in a state of acute alimentary intoxication, when its values were high. In all but one of our cases of intoxication the urea nitrogen was decidedly more than 50 per cent. of the total. The blood of the first three children was obtained within twenty-four to forty-eight hours before death; in the other cases it was obtained at least three days before death.[21]

CONCLUSIONS

1. The blood of infants recovering from the milder intestinal disorders contains between 20 and 30 mg. of nonprotein nitrogen per 100 c.c. as determined by the method of Folin and Denis, agreeing with the values obtained by several authors for normal individuals. The urea nitrogen forms about 50 per cent. of the nonprotein nitrogen.

2. In atrophic infants the nonprotein nitrogen frequently exceeds 30 mg. per 100 c.c. of blood, and these findings seem to be associated rather frequently with a bad prognosis.

3. A low urea nitrogen associated with a low nonprotein nitrogen in atrophic infants seems to be a favorable sign.

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21. Dumitrescu and Popescu (Zentralbl. f. Biochem. Biophys., 1915, **18,** 184. Abstr., Chem. Abstr., 1916, **10,** 931) described a very marked increase of the total nonprotein nitrogen and urea in the blood shortly before death in patients suffering for some time of disease other than renal. The original paper is not at our disposal and the abstract does not contain any further data of use to us in this connection. Among some determinations in various conditions we have one made on an infant of 9½ months, weighing 16 pounds, which died of a capillary bronchitis on the day the determination was made. The nonprotein nitrogen was 24 mg., the urea nitrogen 13 mg., that is, there was no increase.

THE NITROGEN PARTITION IN THE URINE OF NORMAL CHILDREN *

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From time to time the need has arisen in our hospital work of having figures for the nitrogen partition in the urine of normal children, as a basis for comparison with figures obtained from patients with pathologic conditions. While there is no reason to presuppose that such figures would vary grossly from those for the nitrogen partition in the adult, in many respects children form a distinct group of individuals in so far as their metabolism is concerned. As evidence of this we might cite the increased total energy requirement of the infant and young child, the increased nitrogen retention coincident with growth and development, and the variations in the metabolism of some of the individual nitrogenous substances, as creatinin.

Previous studies of the nitrogen metabolism in children have been concerned with other phases, as for example the utilization of nitrogen and studies on the nitrogen requirements carried out on an individual child over a long period of time. In our problem we are concerned only with the distribution of the total nitrogen in the urine under normal or usual conditions.

DIET

In outlining the study the question of diet and its influence at once arose. It was decided to carry out the work in two parts. In one, a group of children were to be studied who were on a diet corresponding to the usual diet which a healthy child receives. For the second part, a study of the urine of children on a "creatinin-free" diet, and one which could be regulated according to body weight, was outlined. The second gives a better basis for comparative studies.

In outlining the diet for the first group a number of children were watched to see about how much food was taken when they were allowed a free supply, and the amount and proportion taken noted. Fixed quantities by age periods were then determined, and by actual test it was found that these were satisfactory both to the child and from the standpoint of maintaining body weight. We were surprised to note the large protein component in the diet of the average child.

* Submitted for publication Jan. 29, 1917.
* From the Department of Pediatrics, Washington University Medical School, and the St. Louis Children's Hospital.
* Read before the Annual Meeting of the Central States Pediatric Society, St. Louis, Oct. 18, 1916.

The diet as outlined approximates very closely the diet of the healthy child under average economic circumstances. The diets outlined in this way we term "standard diets," and are as follows:

Diet for Children Between 20 and 36 Months of Age

6 a. m.	250 c.c. milk	Caloric value about 1,000, of which
10 a. m.	Oatmeal *	
	250 c.c. milk	F = 40 to 45%
2 p. m.	2 graham crackers	C = 35 to 40%
	250 c.c. milk	P = 15 to 20%
6 p. m.	1 slice zweibach	42 gm. protein—6.7 N
	1 soft boiled egg	
	250 c.c. milk	

Milk refused during day to be saved and given at night.

Age 3 to 6 Years

Morning	Milk, 250 c.c.	Protein furnishes about 20% of calories
	Oatmeal *	
	1 egg	Protein 52.6 gm. = 8 gm. nitrogen
Midday	Beef stew †	
	Bread, 25 gm.	
	Butter, 10 gm. (may be added to stew)	
	Milk, 200 c.c.	
Evening	Bread, 25 gm.	
	1 egg	
	Butter, 5 gm.	
	Milk, 250 gm.	

Age 6 to 10 Years

Morning	Milk, 250 c.c.	Protein about 58 gm. = 9 gm. nitrogen
	Oatmeal *	
	1 egg	
Midday	Beef stew ‡	
	Bread, 50 gm.	
	Butter, 10 gm. (If child refuses butter on bread put in stew.)	
	Milk, 200 c.c.	
Evening	Bread, 25 gm.	
	Butter, 5 gm.	
	Milk, 250 c.c.	

Age 10 to 14 Years

Morning	Milk, 250 c.c.	Protein equivalent to about 60-65 gm., or nitrogen about 10 gm.
	Oatmeal *	
	1 egg	
	Bread, 25 gm.	
	Butter, 5 gm.	
Midday	Beef stew	
	Bread, 50 gm.	
	Butter, 10 gm.	
	Milk, 25 c.c.	
	Stewed prunes (5)	
Evening	Bread, 50 gm.	
	Butter, 10 gm.	
	Milk, 250 c.c.	
	Eggs, 1	

* Oatmeal: 25 gm. oatmeal, 500 c.c. water; boil in double boiler four hours. Of this use 70 gm. oatmeal mixed with 10 gm. sugar, 5 gm. butter.

† Beef Stew: Stew 50 gm. lean beef cut fine, 30 gm. raw potato cut fine, 5 gm., salt q. s., 250 c.c. cold water; boil thirty minutes and serve entire portion.

‡ Beef Stew: Take 75 gm. lean beef cut in small pieces, add 40 gm. raw potato, 5 gm. butter and salt q. s., 300 c.c. cold water and boil. (Take off cover last five minutes.) Serve entire portion.

For the study of the nitrogen partition on a creatinin-free diet, a diet was devised in which the amount of nitrogen could be more definitely regulated than by a method of age periods, and one which at the same time was free of creatinin. After some experimentation the following diet was devised. It can be given over five- and six-day periods, and is fairly well liked by the children, except for the monotony. A few children were nauseated and vomited after the second day, and so the diet was not as satisfactory as desired. Such children were not utilized for the study.

Whole milk	200 c.c.
Cream, 20 per cent	200 c.c.
Two eggs	
Malted milk	200 gm.
Water to 1,000 c.c.	2 gm.

Each 100 c.c. contains approximately 150 calories; 35 to 40 calories per kilo of body weight are given and the total amount for the day is divided into five portions. Water is allowed freely as desired.

Each 100 c.c. contains approximately: fat, 7.5 gm.; protein, 6 gm.; carbohydrate, 15.5 gm.

METHOD OF STUDY

The method of study was as follows: Each child was placed on a diet as outlined in the foregoing, according to age in Group 1, and according to weight in Group 2, for a period of six days (occasionally five). No urine was collected the first two days. On the third and succeeding days the urine was carefully collected in twenty-four-hour periods. As a rule, no examination was made of the urine of the third day, but the urines of the fourth, fifth and sixth days were analyzed. A few times the urine of the third day was utilized in place of the specimen of the sixth day.

Determinations of total nitrogen were made by the Folin[1] micro-Kjeldahl method, of ammonia by the Folin[2] method, of uric acid by Benedict's[3] modification of the Folin method, of urea by the urease method of Van Slyke,[4] of creatinin and creatin by the Folin[5] method. In a previous paper we have published the results of acetone and betahydroxybutyric determinations on some of the specimens of urine collected for this study.[6] In all, six twenty-four-hour specimens were analyzed.

1. Folin and Farmer: Jour. Biol. Chem., 1912, **11,** 493.
2. Folin and Macallum: Jour. Biol. Chem., 1912, **11,** 523.
3. Benedict and Hitchcock: Jour. Biol. Chem., 1915, **20,** 619.
4. Van Slyke and Cullen: Proc. Soc. Exper. Biol. and Med., Dec. 17, 1913.
5. Folin: Jour. Biol. Chem., 1914, **17,** 469.
6. Veeder and Johnston: Am. Jour. Dis. Child., 1916, **11,** 291.

TABLE 1.—NITROGEN PARTITION BY GRAMS AND PERCENTAGE FOR TWO CHILDREN ON A STANDARD DIET (Group 1)

Date and Age	Amt.	Sp. Gr.	Total Nitrogen	Ammonia Nitrogen	Urea Nitrogen	Creatinin Nitrogen	Creatin Nitrogen	Uric Acid Nitrogen	Per Cent. of Total Nitrogen					
									Urea	Ammonia	Creatinin	Creatin	Uric Acid	Undetermined
I. 21 mo.														
10/27–28	750	1.012	4.480	0.173	3.941	0.050	0.037	0.060	87.8	3.9	1.1	0.8	1.3	5.1
10/28–29	550	1.018	4.425	0.176	3.852	0.047	0.027	0.050	87.0	4.0	1.1	0.6	1.1	6.2
Average	650	1.015	4.45	0.175	3.897	0.049	0.032	0.055	87.4	3.9	1.1	0.7	1.2	5.7
II. 9 yrs.														
11/ 9–10	440	1.030	7.936	0.354	.....	0.165	0.112	0.069	....	4.5	2.1	1.4	0.9	
11/10–11	410	1.030	8.064	0.325	6.717	0.162	0.098	0.052	83.5	4.0	2.0	1.2	0.6	8.7
Average	425	1.030	8.000	0.340	6.717	0.164	0.105	0.060	83.5	4.2	2.0	1.3	0.8	8.2

RESULTS. STANDARD DIETS

In order to avoid the confusion of too many figures we will give first a detailed result of the analyses of the urine in two children, and then the average percentage partition for the entire group. Table 1 shows the figures obtained in a child of 21 months and in a child of 9 years.

TABLE 2.—PERCENTAGE DISTRIBUTION OF THE NITROGEN IN THE URINE OF CHILDREN ON A STANDARD DIET

Age	Amt. 24 Hours	Total Nitrogen	Per Cent. of Total Nitrogen						Nitrogen Intake
			Uren	Ammonia	Creatinin	Creatin	Uric Acid	Undetermined	
19 months	845	4.43	85.8	6.5	1.2	0.6	2.0	3.9	6.27
21 months	650	4.45	87.4	3.9	1.1	0.7	1.2	5.7	6.71
24 months	480	3.72	81.0	8.5	1.0	1.1	1.4	7.0	6.71
34 months	640	4.88	87.7	4.2	1.0	0.9	1.1	5.1	6.71
4 years	550	6.69	86.0	4.1	1.4	1.0	1.0	7.5	8.10
4 years	690	7.67	85.0	3.5	1.3	1.5	1.2	7.5	8.10
7 years	440	6.26	78.5	5.9	2.1	1.5	1.4	10.6	9.25
9 years	335	5.78	83.0	4.5	2.1	0.5	1.7	8.2	9.25
9 years	425	8.00	83.5	4.2	2.0	1.3	0.8	8.2	9.25
10 years	980	11.50	86.5	3.2	0.8	2.2	1.0	6.4	10.16
10 years	775	7.30	82.0	4.6	2.2	1.9	1.2	8.1	10.16
12 years	435	8.13	82.0	3.7	2.7	1.3	1.3	9.0	10.16
11 years	710	7.22	81.5	3.7	2.3	1.3	1.5	9.7	10.16
Average	...	....	83.7	4.6	1.6	1.2	1.3	7.6	

In Table 2 the figures represent the percentage distribution of each of the nitrogenous substances studied.

They were obtained by averaging the figures for each child obtained by analysis of the daily specimens. It is difficult to get young children to cooperate in metabolic studies, and so we found that the daily variations in the amount of total nitrogen is at times considerable, but the relative amounts of different substances remain practically the same. By averaging the figures for several consecutive days the actual twenty-four-hour partition is obtained with a fair degree of accuracy.

RESULTS WITH CREATININ-FREE DIET

In Table 3 two instances are likewise given of the figures obtained in individual cases from children on the second diet (creatinin-free), in which the quantity given is regulated by the body weight of the child.

TABLE 3.—Nitrogen Partition by Grams and Percentage for Two Children on Creatinin-Free Diet (Group 2)

Date and Age	Amt. 24 Hrs.	Sp. Gr.	Total Nitrogen	Ammonia Nitrogen	Urea Nitrogen	Creatinin Nitrogen	Creatin Nitrogen	Uric Acid Nitrogen	Per Cent. of Total Nitrogen					
									Urea	Ammonia	Creatinin	Creatin	Uric Acid	Undetermined
I. 28 mo.														
11/29-30	860	1.007	3.968	0.214	3.332	0.049	0.079	0.089	84.0	5.4	1.2	2.0	2.2	5.2
11/30-12/1	700	1.012	3.347	0.259	2.778	0.045	0.064	0.099	83.0	7.7	1.3	1.9	2.9	3.2
12/ 1-2	705	1.014	3.676	0.213	3.120	0.052	0.074	0.077	85.0	5.8	1.4	2.0	2.1	3.7
Average	755	1.011	3.663	0.229	3.077	0.049	0.72	0.088	84.0	6.3	1.3	2.0	2.4	4.0
II. 6 yrs.														
11/29-30	770	1.013	4.975	0.205	4.041	0.081	0.064	0.081	81.0	4.1	1.6	1.3	1.6	10.4
11/30-12/1	1140	1.007	4.800	0.213	3.760	0.100	0.038	0.101	78.3	4.4	2.1	0.8	2.1	12.3
12/ 1-2	610	1.013	4.733	0.200	.....	0.095	0.024	0.073	....	4.2	2.0	0.5	1.5	—
Average	840	1.011	4.836	0.201	3.90	0.092	0.042	0.083	80.0	4.2	1.9	0.9	1.7	

TABLE 4.—Showing Percentage Distribution of the Nitrogen in the Urine of Children on a Creatinin-Free Diet

Age	Amt. 24 Hours	Total Nitrogen	Per Cent. of Total Nitrogen						Nitrogen Intake
			Urea	Ammonia	Creatinin	Creatin	Uric Acid	Undetermined	
29 months	755	3.66	84.0	6.2	1.3	2.0	2.4	4.1	3.58
36 months	670	3.48	82.5	4.0	1.7	0.9	2.5	8.4	4.0
6 years	840	4.84	80.0	4.3	1.9	0.9	1.9	11.0	4.37
8 years	465	5.39	86.4	2.7	1.7	1.5	2.0	5.7	6.55
8 years	450	4.56	80.8	4.8	2.4	0.7	2.4	8.9	5.76
9 years	660	4.24	87.0	4.0	2.1	1.0	1.9	4.0	4.70
10 years	860	6.32	85.8	4.0	2.7	0.3	2.9	4.3	6.55
14 years	755	5.89	83.5	3.1	2.6	1.1	1.5	8.2	8.35
Average	...	....	83.7	4.1	2.0	1.0	2.2	7.0	

In Table 4 the average percentage distribution of the nitrogen in the urine is shown for eight children of different ages, in whom the nitrogen partition was studied on the creatinin-free diet. These figures were obtained in the same way as those in Table 2.

In all but two of the children studied there was a positive nitrogen balance which, as a rule, was rather large. The two children with a negative balance were very well nourished. In the group on the creatinin-free diet in which the nitrogen was proportionate to the body weight of the child, and the protein furnished 15 per cent. of the calories, the positive balance was smaller and more uniform, due to the smaller nitrogen intake.

TABLE 5.—Comparison of Creatinin-Free and Standard Diet Groups

	Urea	NH_3	Creatinin	Creatin	$Cr_1 + Cr_2$	Uric Acid
"Cr_1-free" diet group.....	83.7*	4.1	2.0	1.0	3.0	2.2
Standard diet group.....	83.7	4.6	1.6	1.2	2.8	1.3

* Figures represent per cent.

Despite the marked difference in the diet in the two groups, the percentage partition of the nitrogen is strikingly similar, as is shown by comparing the averages of the two groups.

The only marked difference in the percentage distribution between the two groups lies in the amount of uric acid, which was considerably less in the urine of the children on the standard diet.

Urea and Ammonia.—It is interesting to note that in both groups the percentage of urea nitrogen is the same. On the creatinin-free diet the minimum and maximum figures are 80 and 87, respectively, and on the standard diet, 78.5 and 87.7. In only one instance was the amount under 80 per cent. The average figure is 83.7 per cent., which is somewhat less than the average of 87.5 per cent. obtained by Folin in studies on adults.[7] It must be taken into consideration that the method of determining the urea differed in the two studies. The decrease in the percentage of urea is not due to an increased percentage of ammonia nitrogen, as the figures for ammonia nitrogen, 4.1 and 4.6, respectively, in the two groups are approximately the same as the figure (4.3 per cent.) for adults. The difference is due to an increase in the amount of undetermined nitrogen. The ammonia percentage in the urine of children shows a wider range of fluctuation from the mean than in adults, but as a whole, the majority of the figures come very close to the average figure. As increased ammonia nitrogen is usually at the expense of the urea nitrogen, it is interesting to note that the combined urea + ammonia N figure averages about 88 per cent., or under 90 rather than above 90, as is the case in the adult.

Creatin and Creatinin.—The well known observation that creatin is found in the urine of children is borne out by our studies. It was found in every case, although some of the children were approaching puberty, and on an average formed a little over 1 per cent. of the total nitrogen. Little if any decrease occurred in the older children.

Relatively, the amount of creatinin is not as large as in the adult. It averaged about 2 per cent. of the total nitrogen in the children on a creatinin-free diet and a little less than that on a standard diet. In adults about 3.5 per cent. of the total nitrogen is in the form of creatinin nitrogen. This figure is more nearly approached by the combined creatin N + creatinin N figure. We noted a tendency for this combined figure to increase with age (body weight), and it is quite constant in a given individual from day to day. We know that in adults the creatinin elimination on a creatin-creatinin-free diet is quite constant both daily and hourly, but is not constant in relation to body weight, although this is a determining factor in the creatinin elimination.[7] In the urines studied the creatin N + creatinin N figure seems to bear a more definite relation to body weight, averaging between 7 and 8 mg. per kilogram with the child on a creatin-creatinin-diet.

Uric Acid.—The most marked difference between the figures for the partition in the two groups is found in the uric acid. The quantity

7. Folin: Am. Jour. Physiol., 1905, **13,** 45 and 66.

of uric acid eliminated averages nearly twice as much on the creatinin-free as on the standard diet. It forms a little over 2 per cent. of the nitrogen as a rule on the creatinin-free diet, and about 1 per cent. on the standard diet.

SUMMARY

A study of the nitrogen partition in the urine of two groups of healthy children was made to establish normal figures. One group was fed on an ordinary or standard diet containing meat and vegetables, with the quantity regulated by age periods. The second on a creatin-creatinin-free diet in which the quantity of food (and hence of nitrogen) was regulated according to body weight. In both groups the N partition was practically the same, with the exception of the uric acid nitrogen. Urea N makes up from 80 to 85 per cent. and ammonia N from 3 to 5 per cent. The combined figure for the two is less than 90, rather than above 90, as in adults. Creatin is constantly present, as is creatinin. The two combined form a smaller percentage than the creatinin alone in the adult. The amount of undetermined or "rest" N is high in children.

GESTATION VERSUS STAGE OF LACTATION AS FACTORS CAUSING ABNORMAL COMPOSITION OF COW'S MILK*

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All regulations[1] standardizing cow's milk for human consumption exclude its use for a period of time before parturition, the period varying from fifteen to sixty days. Standards of this character are based on the supposition that pregnancy influences the normal composition of milk; in other words, that the milk no longer has a normal composition after gestation has reached a certain stage. The evidence on which this supposition is based is, however, extremely difficult to find, although the literature is extensive with regard to variations in the composition of milk.

The question of the factors influencing the normal composition of cow's milk has for several years been the object of critical study by the Missouri Agricultural Experiment Station. Certain portions of data, which were obtained for another purpose,[2] give a clearer insight into the importance of gestation as a factor causing milk of abnormal composition than any data yet published on this question. It is the purpose of this paper to present those data, together with some additional data, which have a bearing on the question of whether it is the stage of the gestation period or the stage of the lactation period which is the important factor causing milk of abnormal composition as the cow approaches parturition.

SOURCE AND CHARACTER OF DATA

The data presented represent the analyses of the milk and milk fat during the last days of the lactation period of twelve cows, representing four breeds, namely, Jersey, Holstein, Ayrshire and Shorthorn. The analyses for each sample of milk are more complete than any so far

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1. For example, the standards adopted for "Certified Milk" by the American Association of Medical Milk Commissions (Proc. Sixth Ann. Conference, Am. Assn. Med. Milk Comm., 1912, p. 124) exclude the milk for a period of forty-five days before parturition.

2. Eckles, C. H., and Shaw, R. H.: Influence of the Stage of Lactation on the Composition and Properties of Milk. U. S. Department of Agriculture, Bureau of Animal Industry, Bull. 155, January, 1913.

reported bearing on this question. All the cows were pure-bred dairy animals. All except one, Cow 22, received the same uniform ration for the entire lactation period from which the data are taken. The ration consisted of choice alfalfa hay and a grain mixture of corn 8 parts, bran 1 part and oats 1 part. Cow 22 was on pasture with additional grain at the time the data were taken. All the cows were pregnant with the exception of Cow 118. Complete analyses are reported for both the milk and milk fat. For the milk the data include the specific gravity and the percentage of total solids, fat, lactose, total protein and casein. The data in regard to the milk fat include the following physical and chemical constants: saponification value, Reichert-Meissl number, iodin-absorption value, and melting point. The methods of analyses used were those of the Association of Agricultural Chemists.[3]

DESCRIPTION OF TABLES

In Table 1 is presented the composition of the milk and milk fat for a seven-day composite at the close of the lactation period of each of the cows, in comparison with the true average composition for the entire lactation period. The latter values for each cow follow the letter (a), while the values for the seven-day composite at the last of the lactation period follow the letter (b). For several of the cows the last day of the seven-day composite was the last day of the lactation period. Some of the others were milked for a few days longer, this amounting to seventeen days in the case of Cows 300, 301 and 118. Two of the animals, namely, Cows 4 and 403, were milked for several weeks after the last sample was taken, Cow 4 being milked for four weeks, in fact up to the next parturition, and Cow 403 for five weeks. The data from the several cows are arranged in the order of the number of days before parturition when the last samples of milk and butter were taken for analysis. This varied in the different cows from thirteen to ninety-three days.

The figures following the letter (c) for certain of the animals are data similar to those following (b), the difference being that they represent a seven-day composite ending forty-five days before parturition. These data are given for purposes of comparison with the regulations of the American Association of Medical Milk Commissions.

Some additional data are given in the table, such as, (1) the stage of the lactation period when the samples were taken, (2) daily milk flow of each cow at the beginning of lactation and at the time the samples were taken, with the percentage drop, and (3) the length of time each cow was dry before the next parturition.

3. U. S. Department of Agriculture, Bureau of Chemistry, Bull. 107 (Revised), 1908.

TABLE 1.—Relation of Stage of Lactation and Gestation to the Composition and Properties of Milk and Milk Fat

Cow	Time Before Parturition of Sample, Days	Stage of Lactation of Sample, Days	Milk Flow per Day			Time Dry, Days	Composition of Milk						Relation of Casein to Total P., per Cent.	Composition of Milk Fat			
			At First, Lbs.	At End, Lbs.	Drop, per Cent.		Sp. Gr.	Total Solids, per Cent.	Lactose, per Cent.	Fat, per Cent.	Total Protein, per Cent.	Casein, per Cent.		Saponification Value	Reichert-Meissl No.	Iodin Value, Hübl	Melting Point, C.
209 (a)	.....	...	....	....	....	..	.....	11.35	4.25	3.10	3.21	2.49	77.5	229.1	24.44	35.48	32.0
209 (b)	13-20	351	34.2	6.9	79.9	13	1.0344	13.43	4.52	4.01	4.60	3.64	79.1	215.8	20.93	39.06	37.8
209 (c)	45-52	319	34.2	10.6	71.1	..	1.0344	13.70	4.57	3.75	4.66	3.77	80.8	221.4	22.28	36.63	34.4
205 (a)	.....	...	....	....	....	..	.....	12.12	5.05	3.23	3.00	2.49	83.0	228.2	25.81	34.46	33.8
205 (b)	19-26	394	26.3	4.8	81.7	12	1.0332	13.08	4.22	3.53	4.53	3.83	82.1	204.3	10.09	42.22	47.3
205 (c)	45-52	368	26.3	9.4	64.2	..	1.0330	13.54	5.10	3.61	3.96	3.51	88.7	200.1	7.63	44.96	52.9
22 (a)	.....	...	....	....	....	..	.....	15.35	5.26	5.18	4.03	3.16	78.5	232.4	28.85	28.62	23.2
22 (b)	25-27	354	11.4	3.1	73.7	20	1.0357	16.11	4.50	5.35	5.30	4.08	77.0	211.4	12.05	41.53	31.9
22 (c)	45-52	334	11.4	9.3	18.4	..	1.0314	14.84	5.25	4.98	3.88	3.08	79.4	224.4	20.49	41.53	34.2
99 (a)	.....	...	....	....	....	..	.....	13.34	4.95	4.64	3.27	2.65	81.0	228.6	28.69	28.87	33.0
99 (b)	25-32	334	23.6	4.5	80.9	21	1.0349	16.24	6.20	6.07	4.34	3.45	79.5	217.7	14.64	31.12	34.6
99 (c)	45-52	314	23.6	7.9	66.5	..	1.0323	14.85	4.78	5.42	3.89	3.19	82.0	224.0	23.60	30.45	35.0
4 (a)	.....	...	....	....	....	..	.....	14.09	4.85	4.87	3.70	2.93	79.2	231.3	28.17	29.99	32.9
4 (b)	28-35	298	25.7	12.6	50.9	0	1.0340	14.80	4.42	5.62	4.27	3.38	79.0	227.6	25.87	32.18	33.0
4 (c)	45-52	282	25.7	11.4	55.6	..	1.0340	14.55	4.44	4.52	4.46	3.38	75.8	227.2	26.50	32.62	33.2
403 (a)	.....	...	....	....	....	..	.....	12.17	4.98	3.37	3.28	2.62	79.8	227.9	26.29	34.72	32.9
403 (b)	53-60	312	30.3	4.1	86.5	19	.....	13.31	4.40	4.10	4.08	3.13	76.7	224.9	23.03	35.88	33.3
300 (a)	.....	...	....	....	....	..	.....	12.08	4.85	3.51	3.11	2.62	84.2	228.4	26.34	31.14	33.8
300 (b)	75-82	281	27.9	3.1	88.6	58	1.0340	14.14	3.74	4.65	4.60	3.90	84.8	216.7	17.43	39.64	33.3
402 (a)	.....	...	....	....	....	..	.....	13.01	4.91	4.13	3.49	2.87	82.2	226.9	25.55	34.09	33.4
402 (b)	79-86	279	21.6	3.2	85.2	79	1.0314	13.37	4.14	4.50	4.53	4.15	91.6	210.4	14.98	41.33	37.1
400 (a)	.....	...	....	....	....	..	.....	13.08	5.04	3.89	3.40	2.74	80.6	227.6	26.89	34.08	33.6
400 (b)	83-90	308	22.7	4.3	81.0	83	1.0303	12.79	4.29	4.20	3.70	3.45	93.3	216.5	22.41	38.77	36.6
206 (a)	.....	...	..	....	....	..	.....	10.73	4.26	2.93	2.70	2.11	78.1	230.1	26.13	32.68	32.9
206 (b)	83-90	310	45.4	4.5	90.1	73	1.0346	13.95	4.48	3.73	4.91	3.89	92.8	215.4	15.27	37.62	35.2
301 (a)	.....	...	....	....	....	..	.....	12.71	4.96	3.85	3.33	2.81	84.5	227.9	25.52	32.06	33.2
301 (b)	93-100	359	20.4	4.6	77.5	76	1.0375	13.02	4.90	4.48	4.41	3.83	87.1	219.5	18.58	36.35	33.7
118 (a)	.....	...	....	....	....	..	.....	15.02	4.80	5.36	3.97	3.13	78.9	227.2	23.28	32.79	33.0
118 (b)	Farrow	394[1]	14.3	6.6	53.8	..[2]	1.0370	17.97	5.11	7.39	4.85	3.64	75.0	216.5	11.70	32.41	37.4

1. Cow in milk 411 days. 2. Cow not in milk again.

In Table 2 is shown the relation of the time before parturition to certain abnormalities in the composition of the milk and milk fat of each animal. The characteristics of the milk considered in this table are the percentage of total protein and fat, and the Reichert-Meissl number of the milk fat. The standards chosen as the limits of normality are 4.5 per cent. fat and 4 per cent. protein,[4] and a minimum Reichert-Meissl number of 24.00[5] for butter fat. The time given in the table is the number of days before parturition when the three characteristics passed beyond these limits of normality.

TABLE 2.—RELATION OF TIME BEFORE PARTURITION TO ABNORMAL MILK

Cow	Protein, per Cent.	Time, Days	Fat, per Cent.	Time, Days	Reichert-Meissl Number	Time, Days
209	4.15	62	6.54	23	20.31	107
205	4.02	29	....[1]	...	21.83	99
99	4.08	55	....[2]	...	23.60	62
4	4.21	49	....[2]	...	.....[3]	...
403	4.08	60	....[1]	...	23.03	49
300	4.08	92	....[1]	...	23.25	113
402	4.08	110	4.71	110	22.38	145
400	....[4]	...	...[1]	...	23.33	128
206	4.15	107	....[1]	...	23.08	135
301	4.15	103	....[1]	...	22.26	110

1. Did not exceed 4.5 per cent.
2. Animal normally tested over 4.5 per cent.
3. Did not go lower than 24.00.
4. Did not exceed 4.0 per cent.

DISCUSSION OF DATA

An examination of Table 1 with the above standards in view shows at once that the stage of the gestation period bore no relation to the time the milk and milk fat passed the limits of normality chosen for comparison. Only a few specific citations are necessary to establish this fact. For example, both the milk and milk fat showed greater abnormalities in composition in the case of Cow 206 when she was three months from parturition than in the case of Cow 209 when she was only two weeks removed from parturition. Again, no greater abnormalities in composition of milk and milk fat are shown in the

4. These are the standards for certified milk of the American Association of Medical Milk Commissions, adopted as those best suited for purposes of diet and nutrition.

5. The minimum legal standard for butter fat of the United States Pure Food Laws.

entire table than by Cow 118, which was farrow. Finally, the samples which show the least abnormality are those from Cows 4 and 403, particularly with respect to the composition of the milk fat. It was these animals whose milking period was continued the longest after the last sample was taken for analysis, this being four weeks in the case of Cow 4, and five weeks in the case of Cow 403. It is clear that when the last sample was taken for analysis in the case of these animals neither of them had reached a stage in their lactation period which corresponded with that of the other animals from which data are presented.

An interesting feature of the table is the relation between the casein and total protein of the milk at the time the last sample was taken, in comparison with the relation which prevailed throughout the entire lactation period. The data show that in most cases the same relation existed at the close of lactation as throughout the lactation period, indicating that the protein increase in milk, which is characteristic of advancing lactation, is more or less of a concentration of protein constituents and not essentially an increase in the output of casein.

It is also clear from Table 1 that for seven of the twelve animals the milk passed the limits of normality chosen for comparison long before they had reached that stage of gestation, that is, forty-five days before parturition, which is most commonly recommended as that beyond which cows no longer give normal milk. The data in Table 1 following the letter (c) are accordingly given to see whether the forty-five day standard sufficed for the remaining five animals. An examination of these data shows that the milk of Cow 209 would have been excluded with fairness on account of the high protein content and the abnormal composition of the milk fat. The exclusion of the milk of Cows 205, 22 and 99 would not have been fair, however, on the basis of percentage of protein, which was in each case within the limits of normality chosen. An exclusion of the milk of these cows on the fat percentage basis would also have been unfair although the fat exceeded 4.5 per cent. in the case of Cows 22 and 99. These two animals were Jerseys, and their milk normally tested in excess of the 4.5 per cent. standard. It is worthy of note, however, that the milk fat of all three animals was abnormal in composition, particularly Cow 205. In the case of Cow 4 the exclusion of the milk at this time with fairness would also have been very questionable inasmuch as the milk was still following closely the average composition of the lactation period in all respects with the exception of a slightly increased total protein. It may be pointed out in connection with the data considered under (c) that each cow was still giving a gallon or more of milk a day. Dairy

cows giving this quantity of milk are found in the herds of most dairymen, for it is the usual practice to continue the milking period as long as possible.

While considering the question of the standard of forty-five days before parturition, it is of interest to ascertain the length of time before parturition when the milk of the animals under discussion passed the limits of normal composition with which our data have been compared. This point is considered for certain of the animals in Table 2. The wide variation between the individual animals, and also from the forty-five day standard, is very striking.

DISCUSSION OF RESULTS

It is important to state that the data and discussion presented in this paper are not offered in any sense in criticism of the standards of normality with which the data have been compared. These standards have been used for comparison because they were adopted with the problem of infant feeding especially in view, and because we believe our data have particular bearing on that problem. We believe, however, that the standards might well be extended to include the composition of the milk fat as indicated by some one or more of the chemical or physical constants. Unfortunately, no information is at present available in regard to the relation of the composition of the fat of cow's milk to its suitability as food for infants, or as a matter of fact, for human food in general. It is clear, however, to any one who studies the question with an open mind, that it is easy for the dietitian to remedy an abnormal percentage of the milk constituents by the usual methods of modifying milk for infant feeding. An abnormal composition of the milk fat, however, cannot be corrected by these means.

The question on which our data have particular bearing is whether any milk standards are justified in excluding milk for use on the basis of the stage of the gestation period. Our data seem to us to show clearly that this is not the correct basis. The abnormalities to which cow's milk is subject when parturition is approaching are due largely, if not entirely, to the stage of the lactation period. The data here presented indicate clearly that cow's milk becomes abnormal in composition as soon as the lactation stimulus becomes an artificial one on the part of the dairyman, and that this result bears no relation to the stage of the gestation period. Many cows show these abnormalities several months before the next parturition, while very heavy producing cows with periods of parturition the usual interval of twelve to thirteen months apart, may continue to produce perfectly normal milk up to the very hour of the next parturition. The latter are the exception, however, rather than the rule. The great majority of dairy cows in

this country are relatively small producers. In these cases the high protein and fat content, and abnormal composition of the milk fat characteristic of the end of the lactation period may become important questions in connection with infant feeding long before the forty-five day limit is reached. Where mixed milk of a large herd is used the danger of wide variations due to the end of the lactation period would naturally be less likely to occur. The great danger lies in the small herd of cows which are likely to freshen about the same time of the year, and especially in the case of the family cow, in both of which cases the common practice is to continue milking the animals as long as possible.

To those who may desire to make use of the facts here presented, one very practical question arises in this connection, namely, what criterion is available by which the end of the lactation period can be judged? The percentage decrease in the milk flow from that when the cow was fresh is some indication of the stage of the lactation period. This information was given in connection with the data in Table 1 with this point in view. The relations are not definite enough, however, for the establishment of any safe rule that can be followed. Moreover, this information would usually be difficult to secure with accuracy. The milk from cows giving as low as a half-gallon a day should certainly be regarded with suspicion, and should be subjected to critical analysis, especially where the feeding of infants and children is concerned.

Dairy Building.

THE BACTERIOLOGY OF THE URINE IN CHILDREN WITH VULVOVAGINITIS

WITH A REPORT OF TWO CASES OF GONOCOCCUS CYSTITIS *

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The conception of an ascending route of infection in cystitis of infancy has heretofore largely rested on the unproved assumption of a constantly contaminated urethral tract. Such a hypothesis served to explain the predominance of cystitis in female infants. Helmholz and Beeler[1] in a recent study of the bacteriology of the urine in normal children, and of the urine from children with extra-urinary infections, established conclusively that the organisms of the colon group are not normal inhabitants of the female urethra. They further demonstrated that in those instances of extra-urinary infection in which organisms were found in the urine, these were present in such small numbers that they could not be considered other than accidental contaminations from the urethra.

If the incidence of cystitis were subject to local factors, then any condition which increased such local factors should militate against a sterile urinary tract. It therefore seemed important to study the bacteriology of the urine in children with vulvovaginitis. For we have in this disease inflammatory changes the contiguity of which to the urethra might conceivably produce a *locus minoris resistentiae*, which would favor contamination of the urinary tract with resulting cystitis. The bacteriology of the urine from eighteen unselected patients with chronic gonococcus vulvovaginitis was studied. These patients were all over 2 years of age. Catheterized specimens were obtained and cultures made, using the technic and method described by Helmholz and Beeler.

Two specimens were obtained from each patient, the first representing approximately the flora of the urethra, the second that of the bladder. A portion of the first specimen was examined for albumin, another part centrifuged and examined in stained smears for bacteria and unstained for cellular elements.

At the time of catheterization, thirteen of these eighteen patients presented more or less vaginal discharge, and all of the eighteen had leukocytes in their vaginal smears. Only five showed gonococci in the vaginal smears at the time of catheterization. None of these eighteen

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* Submitted for publication Jan. 18, 1917.

* From the Otho S. A. Sprague Memorial Institute Laboratory of the Children's Memorial Hospital, Chicago.

1. Beeler, C., and Helmholz, H. F.: Bacteriology of the Urine in Healthy Children Suffering from Extra-Urinary Infections, AM. JOUR. DIS. CHILD., 1916, **12,** 345.

TABLE 1.—Bacteriology of the Urine in Cases of Vulvovaginitis

Case No.	Vulvovaginal Findings			Urine Examination		Cultures of Specimen 1		Cultures of Specimen 2		Remarks
	Discharge	Leukocytes	Gonococci	Albumin	Microscopic	Colonies per C.c.	Types of Organisms	Colonies per C.c.	Types of Organisms	
1	+	+	+	–	Negative.....	10	Staphylococcus albus; diphtheroid bacillus	Less than 1	Gram + coccus	Diphtheroid bacillus, which constituted majority of colonies, appeared only on a blood agar plate
2	+	+	–	–	Negative.....	0	.....	0	.....	
3	+	+	–	–	Stained sediment shows large gram + coccus	Innumerable	Staphylococcus albus..	Innumerable	Staphylococcus albus..	Identical findings on recatheterization 18 days later
4	+	+	+	–	Negative.....	0	.....	Less than 1	Bacillus subtillis.....	Only 1 colony present, this not appearing until 6th day on blood agar plate
5	–	+	–	Faintest trace	Negative.....	Less than 1	Bacillus subtillis.....	0	.....	Only 1 colony present, this on the blood agar plate
6	–	+	–	–	Negative.....	3	Staphylococcus albus..	10	Staphylococcus albus..	Specimen 2 inoculated in deep dextrose blood agar tube only
7	+	+	–	-	Negative.....	Less than 1	Diphtheroid bacillus; gram + coccus	Less than 1	Diphtheroid bacillus...	
8	+	+	–	–	Negative.....	3	Staphylococcus albus; gram + diplococci	2	Gram + coccus; gram + diplobacillus	
9	+	+	+	–	Negative.....	Less than 1	Bacillus subtillis.....	1	Staphylococcus albus; gram + diplococcus	
10	+	+	–	–	Negative.....	0	.....	0	.....	
11	–	+	–	–	Negative.....	6	Gram + diplococcus..	6	Gram + diplococcus..	
12	–	+	–	–	Negative.....	1	Gram + diplobacillus; Staphylococcus aureus; diphtheroid bacillus	10	Gram + diplococcus...	Only medium showing growth from Specimen 2 was deep tube of dextrose blood agar
13	+	+	–	–	Stained sediment shows gram — coccus. No cellular elements	0	.....	0	.....	
14	–	+	–	–	Negative.....	3	Diphtheroid bacillus; gram + diplobacillus	0	.....	
15	+	+	–	–	Negative.....	2	Diphtheroid bacillus; gram + diplococcus	0	.....	
16	+	+	–	–	Negative.....	0	.....	0	.....	Only Specimen 2 cultured
17	+	+	+	+	Large number of pus cells; stained sediment shows leukocytes with gram — diplococci	Less than 1	Staphylococcus albus..	Less than 1	Gram + diplobacillus..	Urine milky; contains flocculi; acid reaction
18	+	+	–	+	Large number of pus cells; stained sediment shows leukocytes with gram — diplococci	Less than 1	Gram — short diplobacillus; would not grow in subcultures	0	.....	Urine milky; contains flocculi; acid reaction

patients, however, had had vaginal smears negative for gonococci for any three consecutive weeks (a requirement prior to discharge of such patients from this hospital).

The bacteriologic findings were as follows: (Table 1) Specimen 1 was sterile in five instances, in ten instances gave less than 3 colonies per cubic centimeter, in one instance 6 colonies per cubic centimeter, in one instance 10 colonies per cubic centimeter, and one showed innumerable colonies. Specimen 2 was sterile in eight instances, gave 1 or an average of less than 1 colony per cubic centimeter in five instances, 2 colonies per cubic centimeter in one instance, 6 colonies per cubic centimeter in one instance, 10 colonies per cubic centimeter in two instances, and one showed innumerable colonies. From the same patient whose urine gave a profuse growth of a *Staphylococcus albus* in both Specimens 1 and 2, subsequent catheterization and cultures brought identical findings. This urine showed no other abnormalities, nor did the particular patient exhibit any subjective evidence of urinary disturbance.

TABLE 2.—Bacteriology of the Urine After Recatheterization

Case No.	Vulvovaginal Findings			Urine Examinations		Cultures	
	Discharge	Leukocytes	Gonococci	Albumin	Microscopic	Colonies per C.c.	Types of Organisms
1	—	+	+	—	Negative.....	2	Diphtheroid bacillus
2	—	+	—	—	Negative.....	2	Staphylococcus albus
3	+	+	—	—	Negative for cellular elements	Innumerable	Staphylococcus albus
4	+	+	+	—	Negative.....	0	
5	—	—	—	—	Negative.....	Less than 1	Diphtheroid bacillus
6	—	+	+	—	Negative.....	0	
7	—	+	—	—	Negative.....	0	
8	—	+	—	—	Negative.....	1	Staphylococcus
9	—	+	—	—	Negative.....	Less than 1	Gram negative bacillus
10	+	+	—	—	Negative.....	Less than 1	Bacillus, gram ±

The character of the organisms obtained were very similar to those reported in the series of normals by Helmholz and Beeler, namely, gram-positive cocci and diphtheroid bacilli. In no instance was a gram-negative bacillus encountered.

In Cases 17 and 18, however, as shown in Table 1, the sediment, even uncentrifuged, showed masses of pus cells, with occasional leukocytes filled with gram-negative, biscuit-shaped diplococci. These two instances will be discussed at greater length in the latter part of this article.

After an interval of several weeks, ten of the patients, who were kept constantly under observation in the interval, were again catheterized, slightly varying the methods of study. In the series of recatheterizations (Table 2; the numbers correspond with case numbers in Table 1) Specimen 1 was used for centrifugation and microscopic study but was not cultured. Specimen 2 was planted on plates of lactose litmus agar and ascites dextrose agar, the former to make identification of any of the colon group easier, the latter for growth of the gonococcus. The total result, practically negative findings in the series of recatheterizations, is a circumstance of striking importance. It is noted that in not a single instance, as shown either by the clinical urinary analysis or by the bacteriologic findings, does the recatheterization reveal any urinary infection which might be conceived as following either the vulvovaginal infection or the first catheterization per se. In only one instance, the patient with staphylococcus bacteriuria mentioned previously, were the bacteria present in such numbers that they could not be considered as accidental contamination from the urethra. Of the ten specimens, three were sterile, all the others but one showing less than 2 colonies per cubic centimeter. The few organisms encountered were either staphylococci or diphtheroid bacilli, except in Case 9, in which the ascitic dextrose agar plate showed one colony, a gram-negative bacillus.

Comparing the results of the present series with those reported by Helmholz and Beeler in children over 2 years of age, a difference is only noted in regard to Specimen 1. Of their series, 83 per cent. showed 1 colony or less per cubic centimeter. In the present series this percentage is 58, giving a smaller number of practically sterile urines in those obtained from patients with vulvovaginitis. In the comparison of the results obtained from cultures of Specimen 2, this difference disappears. Of their series, 73 per cent. showed either a sterile urine or less than 1 colony per cubic centimeter. In the present series 72 per cent. showed the same findings. The negligible difference in results with Specimen 1, is easily explained, in that it is quite conceivable that during a vulvovaginitis, the distal end of the urethra may harbor more bacteria than normally, and Specimen 1 of these respective series represents this flora as well as that of the deep urethra. Specimen 2, however, representing the bladder flora, shows the same comparative absence of organisms in the urine of patients with vulvovaginitis as was demonstrated in that obtained from normal children.

GONOCOCCUS CYSTITIS

Notwithstanding the frequency of gonococcus vulvovaginitis in childhood, particularly as met with in hospital practice, and the numerous reports that have been published regarding this disease, one is

struck with the very meager data at hand regarding gonococcus cystitis in childhood. Statistical tables in the majority of investigations are conspicuously silent on this complication, many not mentioning it, others noting a rare case with few details in a large series of observations. Welt-Kakels[2] notes that gonococcus cystitis is but very rarely observed, having seen only one case in a series of 190 children with vulvovaginitis. Edith Spaulding,[3] reporting 5 cases of cystitis among 74 children with vulvovaginitis, says: "We believe cystitis is much more common than is realized, but as the urine is not examined in every case, it is often not discovered." Neither of these observers states how the diagnoses were reached in their cases. It should be remarked that even with urinalyses, cystitis may be overlooked, the cellular elements encountered being attributed to the vaginal discharge rather to coexistent cystitis. This is probably the most frequent source of error and may account for the infrequency of hospital diagnoses of this condition. In this connection it might also be stated that presence of leukocytes in a vaginal smear, sometimes wrongly interpreted as evidence of a latent vaginitis, may occasionally be due to an undiagnosed cystitis of *Bacillus coli* origin.

In the present series of vulvovaginitis cases two instances of gonococcus cystitis were encountered. It is extremely interesting that both of these patients had had previous infection of the urinary tract, one having entered the hospital with a colon cystitis, the other with a mild nephritis associated with a colon bacilluria, vulvovaginitis developing in both at a later time. Their persistent cystitis had not aroused any suspicion of the true infection until they were catheterized for the purpose of the previous study. Like many other patients with cystitis, there were no subjective complaints. On this catheterization and on later catheterization, the urine obtained in both instances was of a milky character and held suspended numerous fine flocculi. Uncentrifuged smears showed innumerable pus cells, many exhibiting the characteristic inclusion of gram-negative diplococci. It is of course impossible to state when the *Bacillus coli* had been displaced by the gonococcus as the infecting organism. One of these patients was cystoscoped by Dr. Herman L. Kretschmer. The bladder showed a cystitis at the trigonum, the usual pathologic picture of such infections. The ureteral orifices as seen with the plain cystoscope appeared normal.

These instances afford another possible explanation for the occasional protracted case of vulvovaginitis that is refractory to treatment. Such a bladder mucosa might act as a source of reinfection of the vaginal tract.

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2. Welt-Kakels: New York Med. Jour., 1904, **80,** 780.
3. Spaulding, E. R.: Vulvovaginitis in Children, Am. Jour. Dis. Child., 1913, **5,** 248.

The difficulty of cultivation of these organisms from the urine has been noted by Colombini[4] and others. Whether this same slow growth of the gonococcus accounts for the apparent rarity of this organism as a cause of cystitis in children, may only be conjectured. It has been shown by several investigators that the mere presence of the gonococcus in the bladder will not produce a cystitis. In these particular instances the previous infection by the *Bacillus coli* may have produced changes in the bladder mucosa favorable for subsequent infection by the gonococcus.

SUMMARY

In eighteen unselected patients with chronic gonococcus vulvovaginitis, carefully catheterized specimens of urine showed a comparative absence of bacteria. The majority of the organisms encountered were either gram-positive cocci or diphtheroid bacilli. In most instances these were in such small numbers that they could easily be accidental contaminations from the urethra.

The second portion of the urine, representing the bladder flora, was shown to be as free from infecting organisms as was demonstrated in a previous series of normals. The occurrence of vulvovaginitis did not increase the tendency to contamination of the bladder.

Gonococcus cystitis may follow previous infections of the bladder by *Bacillus coli* in patients with vulvovaginitis.

410 Goldsmith Building.

4. Colombini: Quoted by Young, H. H.: Johns Hopkins Hospital Rep., 1900, **9**, 677.

CLINICAL DEPARTMENT

REPORT OF A CASE OF CONGENITAL ENDOCARDITIS

WITH ACUTE VEGETATIVE INFLAMMATION OF THE PULMONARY ARTERY AND VALVE *

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On reviewing the literature pertaining to this subject one is impressed by the infrequency of the condition, and by the large percentage of the cases coming to necropsy undiagnosed.

Hirschfelder[1] reports only three cases of 24,000 medical admissions to the Johns Hopkins Hospital, and of this number only one case was diagnosed during life.

In Abraham's[2] clinic in the New York Post Graduate Hospital, in which nearly 800 cases are studied yearly, only one case of pulmonary insufficiency has been encountered in the past eleven years.

Willigk,[3] in 4,547 dead bodies, found inflammation of the pulmonary valves nine times; twice this valve alone was involved.

Berthram Abraham[4] found, in 300 necropsies held on subjects of heart disease at Westminster Hospital, that thirty-nine showed ulcerative valvular changes. In only one were the pulmonary valves involved, and this involvement was associated with aortic and tricuspid ulceration. Out of 16,000 postmortem examinations at Guy's Hospital[5] only twenty-four showed pulmonary incompetency.

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* Submitted for publication Dec. 22, 1916.
* Read before the Medico-Chirurgical Society, Dec. 8, 1916.

1. Hirschfelder: Diseases of Heart and Aorta, Philadelphia, 1913, p. 480.
2. Abraham, R.: A Case of Pulmonary Insufficiency, Jour. Am. Med. Assn., 1913, **60,** 1150.
3. Willigk: Quoted from Allyn, Insufficiency of Pulmonary Valves, Am. Jour. Med. Sc., 1913, **146,** 541.
4. Abraham, B.: Brit. Med. Jour., 1899, **2,** 1273.

Babcock[5] has encountered in his observation of heart conditions only one case of acute pulmonary endocarditis; even in this one a postmortem was not obtained.

In 846 Munich cases the pulmonary valves in general were involved in 1.54 per cent.; alone in 0.59 per cent.

In Parrot's[6] 1,058 cases of valvular involvement, only 0.01 per cent. showed the pulmonary valve to be affected. On the other hand, Sperling[7] is credited with saying that in 4 per cent. of combined valvular lesions the pulmonary valves are involved in a greater or less degree.

The clinical terms, pulmonary insufficiency, regurgitation, and incompetency, etc., which the above statistics embrace, are commonly used to signify any condition referable to the pulmonary valve. These general terms, as we shall see later, lead one astray, when the true nature of the condition is ascertained. They mean nothing to the internist from the prognostic point of view. To the pathologist they furnish no light as to the etiology of the condition, nor do they convey to the anatomist a congenital deformity, which is so often encountered and referred to in these terms.

Thus, for the sake of clearness, we will classify pulmonary valve conditions into (1) congenital and (2) acquired.

Congenital.—Under the general heading congenital, we have (1) structural changes; namely, maldevelopment, irregularity in form of the valves; (2) organic changes, or fetal endocarditis. Acute fetal endocarditis has never been encountered as far as we have been able to ascertain from the literature. The common form is the sclerotic type, that is to say, the valves are thickened and contracted and the edges often united to those adjoining. The warty variety does occur, but is of far less frequency.

The etiology of fetal endocarditis is not definitely known, but it is thought by some, though hypothetically, that rheumatic fever during pregnancy, or a tendency of the mother to rheumatic attacks, is a cause. Suffice it to say, it is necessarily of chronic origin, as is shown by the diffuseness with which the valves are involved, and by the negative findings of acute manifestations.

We would therefore expect no other etiologic process than a mild, diffusible circulating toxin, filtering through the placental tissue and producing its results by constantly bathing the valves. If this be true, then all the valves of the heart would be more or less affected; however, it is conceded that an anomaly of the heart predisposes the site to attack, and as the right side of the heart is usually the seat of mal-

5. Allbutt's System of Medicine, New York and London, 1906, **6**, 3.
6. Osler and McCrae's Modern Medicine, 1915, **4**, 213.
7. Satterthwaite's Diseases of the Heart and Aorta, New York, 1905, p. 31.

formation in the fetus, it is natural that the right side of the heart should show the highest percentage of involvement. Rauchfuss[8] is credited with saying that the two sides of the heart are equally affected in fecal endocarditis, unless the heart is associated with malformation, in which case the endocarditis is more prominent on the right side.

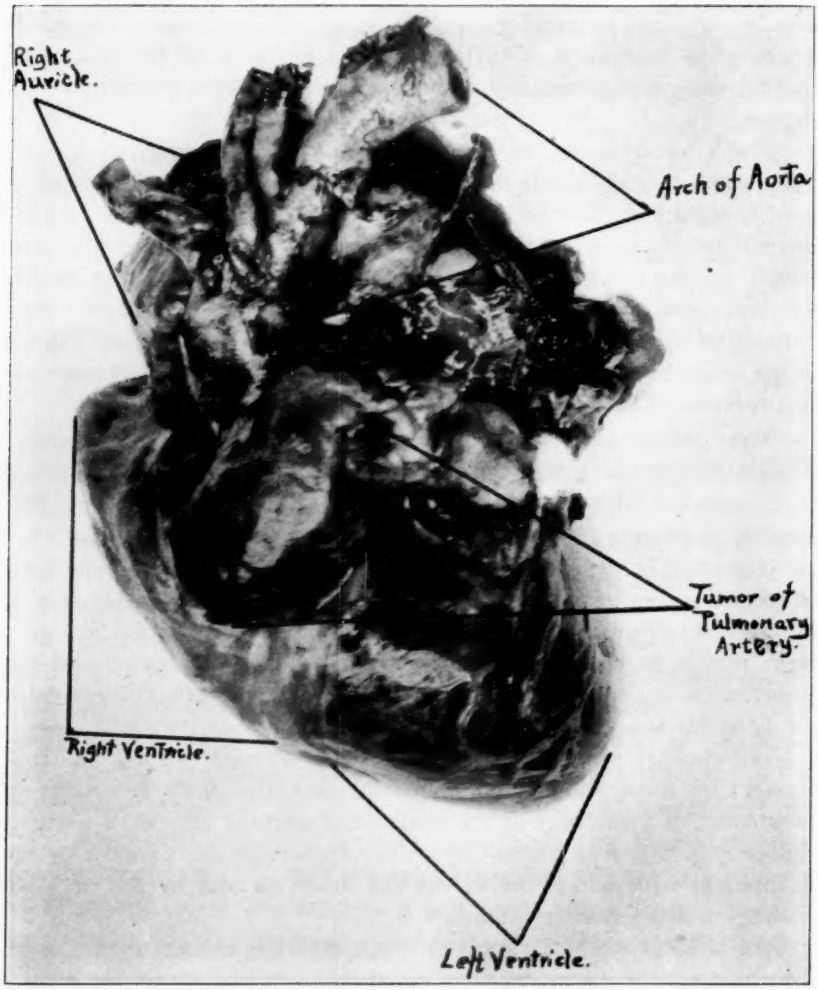

Fig. 1.—Showing the markedly enlarged pulmonary artery (from its origin to its bifurcation).

Acquired Varieties.—Organic Changes:

1. *Acute Infectious Valvulitis.*—This embraces the terms simple, vegetative and ulcerative endocarditis of the valves. There is no

8. Allbutt's System of Medicine, New York and London, 1906, **6**, 5.

definite distinction between these terms. The pathologic process is only one of degree. The etiologic agent, as cultured from the blood, in most instances will reveal the nature of the pathologic picture. That is to say, an endocarditis of pneumococcic or of gonococcic origin has a marked tendency to produce the so-called malignant or ulcerative type of endocarditis.

Acute infectious valvulitis is, according to Pitt,[9] the most frequent cause of pulmonary incompetency. Of the 109 cases of pulmonary incompetency collected from the literature and from Guy's Hospital records by Pitt, 60 cases were of this origin. In 19 of the 51 cases collected from Guy's Hospital reports, lesions of the other valves were associated. That fetal derangement is a factor in subjecting the pulmonary valve to postnatal infection is shown by Pitt's 60 cases of infectious pulmonary valvulitis, in which 21 occurred in a malformed heart, and 8 of the latter were of congenital pulmonary stenotic type.

It may be of interest to show the relative frequency of acute pulmonary valve involvement to other acute valvular conditions, which are summed up in the following statistics: Horder[10] collected from St. Bartholomew's Hospital 115 cases of ulcerative valvulitis; only seven times were the pulmonary valves involved, and then not alone, but each time with the mitral. At the Philadelphia General Hospital,[11] in 8,640 necropsies, 335 showed acute endocarditis; in these the aortic valve was involved 164 times, mitral 143, tricuspid 15, and pulmonary 7. In a review of 1,300 necropsies at the Pennsylvania Hospital,[11] 107 cases of acute endocarditis were found. Valvular involvement was as follows: aortic 25, mitral 47, both 23, aortic, mitral and tricuspid 2, mitral and tricuspid 4, tricuspid 3, pulmonary 1.

Washbourn[12] collected 309 cases of infective endocarditis. As to frequency of attack, the right side was involved alone in 13 cases, mitral alone in 116 cases, aortic alone in 69, aortic and mitral in 73, tricuspid in 28 and pulmonary in 19.

Unfortunately the majority of available statistics which deal with the occurrence of recent endocarditis give no information regarding the microscopic or bacteriologic examination. Among the etiologic agents that are reported in this condition, however, the gonococcus and pneumococcus head the list. In the 60 cases of pulmonary valve involvement reported by Pitt[9] 19 were produced by known organisms. Of the 19 cases, 8 were produced by the gonococcus and 5 by the pneumococcus.

9. Allbutt: System of Medicine, New York and London, 1906, **6,** 3.
10. Horder: Quart. Jour. Med., 1908, **2,** 289 and 324.
11. Norris: Studies in Cardiac Pathology, Philadelphia and London, 1911, p. 26.
12. Washbourn, J. W.: Brit. Med. Jour., 1899, **2,** 1270.

Külbs'[13] analysis of 49 well authenticated cases of gonococcic endocarditis gives the following frequency of valves attacked: aortic 28 times; mitral, 8; pulmonary, 6; tricuspid, 1; aortic and mitral, 3; mitral and tricuspid, 1; all the valves, 1; all except pulmonary, 1.

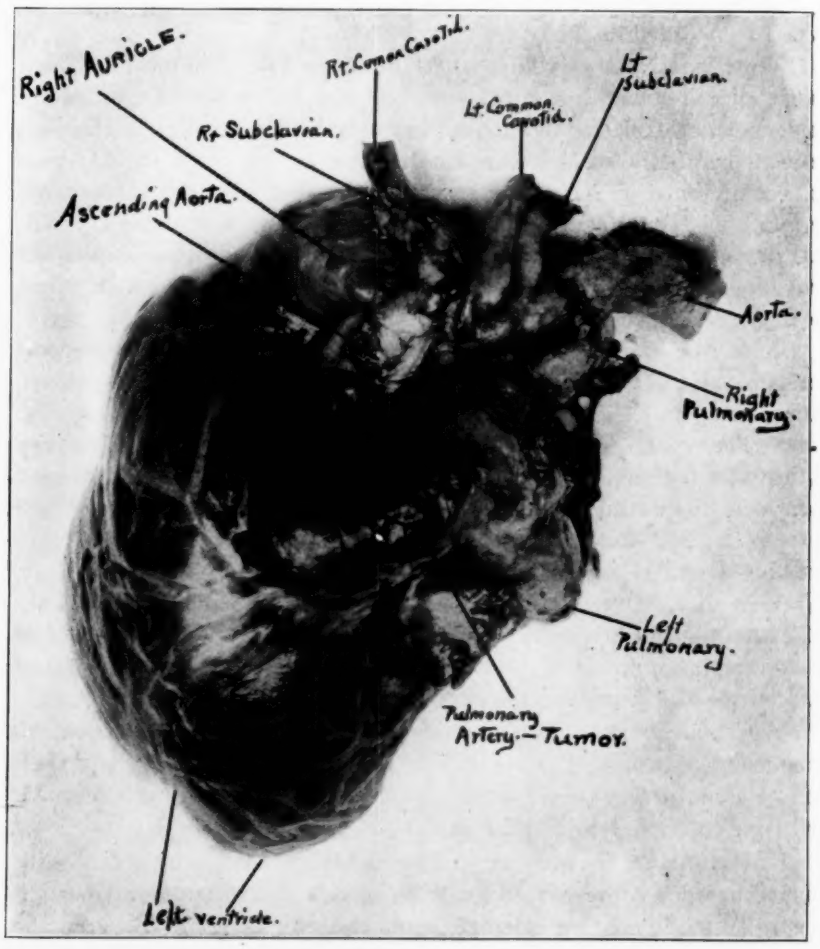

Fig. 2.—Showing the much enlarged right auricle, extending well above the arch of the aorta.

The only case of acute pulmonary endocarditis that was found in the Pennsylvania Hospital records, was of gonococcic origin.

Preble[14] reported five cases of pulmonary endocarditis caused by the pneumococcus.

13. Külbs: Wien. klin. Wchnschr., 1907, **20,** 11. Referred to by Irons, Arch. Int. Med., 1909, **4,** 601.

14. Norris: Studies in Cardiac Pathology, Philadelphia and London, 1911, p. 20.

Callender[15] reported a case of pulmonary valve involvement alone, in which cultures made from the vegetation showed micrococcus endocarditis rugatus.

In valvular involvements other than the pulmonary, the streptococci, the pneumococcus, *Staphylococcus aureus,* colon bacillus, and influenza bacillus in the order named are among the more common etiologic agents. In forty cases reported by Horder,[16] 65 per cent. were of streptococcic origin. In 2,722 pneumonia cases collected by Norris,[17] acute endocarditis was found 158 times. Norris says that the aortic and pulmonary valves are involved more frequently in pneumonia than the other valves, but he does not tabulate their relative frequentcy.

The age distribution in acute pulmonary valve involvement in 49 cases reported by Pitt[3] is as follows: birth to 10 years, 2 cases; 11 to 20 years, 12 cases; 21 to 30 years, 15 cases; 31 to 40 years, 11 cases; 41 to 50 years, 4 cases; 51 to 60 years, 4 cases; 61 to 70 years, 1 case. In comparison with acute valvular lesions in general, Horder[18] found in 150 cases the greatest number between 20 and 30, namely 39; next between 30 and 40, 31; and between 15 and 20, 29 cases. From the statistics, therefore, the most frequent period of involvement of the pulmonary, as well as the remaining valves, is between the ages of 20 and 30.

2. *Chronic Valvular Endocarditis or Sclerosed Valves.*—This condition may be the result of repeated acute attacks, or chronic from the onset, as in the case of arteriosclerosis in general. What is true of other valves is apparently true, in the main, of the pulmonary valves. That is to say, types of sclerosis, from a pathologic standpoint, are much more common, according to the report made by Norris, than the acute variety. Among 8,640 necropsies at Blockley, the pulmonary valves were found sclerosed in forty-four cases, against seven cases that were found to be acutely attacked; whereas Pitt reports, as already noted, that incompetency of the pulmonary orifice is produced more frequently by acute inflammation than any other type of lesion. This apparent discrepancy in the report of necropsy findings is no doubt due to the general use of the term incompetency.

The contrast is more striking in valves other than the pulmonary, as is shown by the figures quoted from Hirschfelder,[19] namely, that only forty-five cases of ulcerative endocarditis occurred among 23,200 admissions as compared with 1,781 of the chronic valvular type.

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15. Callender, S. P.: Am. Jour. Med. Sc., 1915, **149,** 723.
16. Horder: Treatment with Vaccines, Practitioner, 1908, p. 714.
17. Norris: Studies in Cardiac Pathology, Philadelphia and London, 1911, p. 18.
18. Norris: Studies in Cardiac Pathology, Philadelphia and London, 1911, p. 16.
19. Hirschfelder: Diseases of Heart and Aorta, New York, 1913, p. 392.

Sclerosed valves from any cause are more liable than healthy valves to be attacked by infective endocarditis. This is also true of valves in general, as is shown by the following statistics:[12] One hundred and fifty-seven of Osler's 209 cases, 61 of Goodhart's 69 cases, and 59 of Guy's Hospital 100 cases, and 64 of Norris' 107 cases were noted as having old valvulaar disease.

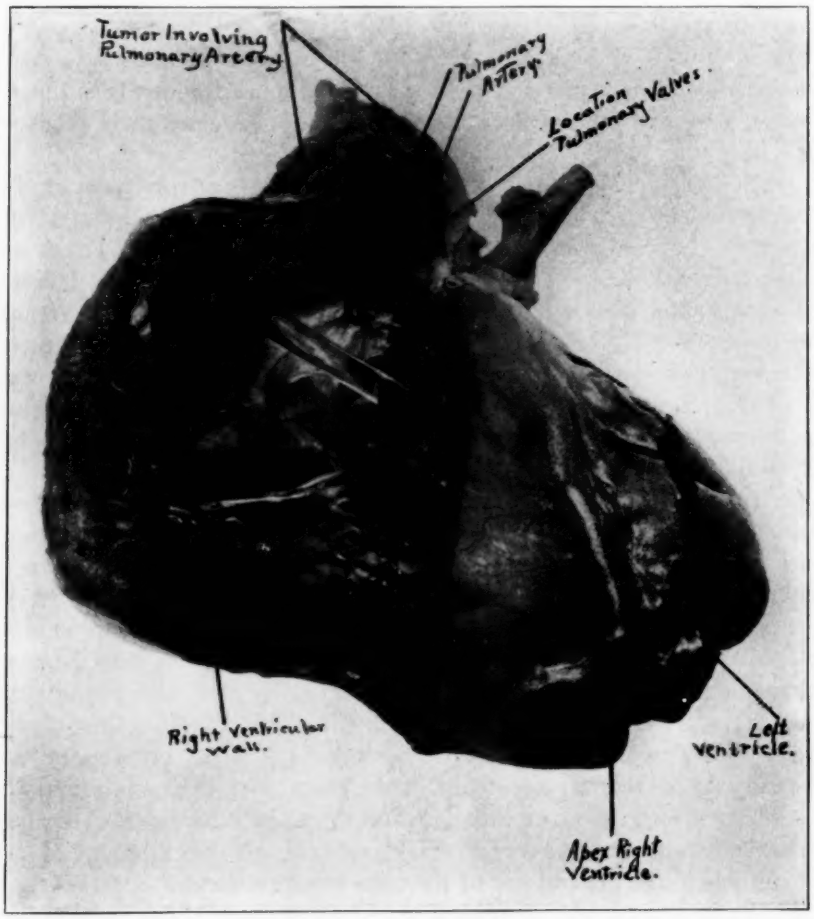

Fig. 3.—Showing the extensive vegetative inflammation of the pulmonary valves and anterior wall of the pulmonary artery, the thickness of the right ventricular wall and the prominence of the apex of the right ventricle.

Relative or functional dilatation of the pulmonary orifice is apart from the purpose of this communication and is therefore omitted.

With the foregoing references to the literature on unusual pulmonary conditions from an etiologic, anatomic and pathologic point of view as a preface, the following case is presented.

REPORT OF CASE

History.—J. H., a boy, aged 13, was admitted to the Orphans' Home, February, 1912, with a certificate from the examining physician to the effect that he was entirely normal in every respect.

The boy's father died in May, 1912, and mother in April, 1913, of tuberculosis. There were six children in the family; three are living and well, and three dead from tuberculosis. No history of any previous illnesses could be obtained either from the family physician or from those connected with him. After admission into the Home, however, the boy was found to be affected with trachoma and hookworm.

Examination on Admission.—On admission, at 9 years of age, physical examination showed him to be of a pasty appearance, undersize and underweight. He was far below the average in intelligence. His facial expression was motionless and mildly hideous. There were a bulging of both eyes, a congenital ptosis of the upper eyelids, bifurcated uvula, and two lower central incisor teeth of the typical Hutchinson type, while the upper central incisors were absent. The entire musculature of the body was undeveloped. There was clubbing of the fingers. The chest showed a prominent cone-shaped bulging of the sternum together with the costal arch on either side, the summit of which was located about the right third costosternal articulation.

A distinct systolic heaving and diastolic retraction of the intercostal spaces were noticed throughout the precordial area, being more pronounced in the second and third interspaces some distance to the left of the sternum. A slight pulsating mass was evident in the neck, situated behind the suprasternal notch. On palpation, a thrill, systolic in time, could be felt throughout the precordial area, being more pronounced in the first, second and third interspaces, just to left of sternum. With the finger tip, a perceptible thrill could be felt over the pulsating mass in the neck.

Percussion revealed an enlargement of the heart to the right of the sternum, and the apex in the nipple line. On auscultation a loud, blowing systolic, and a relative weaker diastolic, murmur were heard over the entire chest anteriorly, being more intense over the second space just to left of the sternum, and slightly diminished along the left border of the sternum to the apex of the heart. A distinct systolic bruit and a low blowing diastolic murmur were heard over the pulsating mass behind the suprasternal notch. There were no murmurs transmitted into the vessels of the neck. Radial and carotid pulses were equal in force and rhythm on both sides. The radial pulse was of good volume. A roentgenogram taken at this time by Dr. E. T. Bruce revealed a shadow to the right and above the outline of the heart.

Subsequent Course.—For the three years following his admission there was little development, either mentally or physically. He was able to play with his associates, but would become dyspneic on the least exertion. The pulsating mass behind the suprasternal notch grew larger and the precordial bulging became progressively greater.

June 11, 1916, the patient showed drowsiness and loss of appetite. The following day he developed a troublesome cough, together with bleeding of the nose and vomiting. The temperature was irregular until two days later, when it rose to 103 F., fluctuating between 100 and 103 F. for the ensuing three weeks; pulse ranged between 90 and 110; respirations between 30 and 40. On the fourth day of the illness there developed a consolidation of the left apex. Over this area fremitus was increased and the breath sounds were bronchial in type.

The blood count showed a leukocytosis; blood culture showed the pneumococcus. The Wassermann was negative.

A tracing made from the radial artery by Dr. Zahner two weeks after the initial onset showed an alternating pulse, which was interpreted by Dr. Greiwe to be of fatal omen. The tracing showed nothing else of interest.

On the twenty-fourth day of the illness, the temperature dropped to normal, but rose on the following day to 101 F., and fluctuated daily in this manner until death, which occurred six weeks after the initial onset. After the first drop in temperature, the original apical consolidation cleared up somewhat, but there remained a distinct impairment of resonance. During the fifth week of illness, distinct cavernous breathing was elicited over the right apex. The heart murmurs, as far as we were able to judge, remained constant both as to intensity and time. The same can be said of the murmurs in the pulsating mass behind the suprasternal notch.

Necropsy.[20]—Necropsy conducted seven hours postmortem. The body is that of a poorly developed, emaciated, white adolescent; edema absent. The marked bulging of the chest anteriorly and clubbing of fingers and toes have already been described.

Heart: Weight 350 gm. The right auricle is markedly enlarged, extending behind and well above the arch of the aorta. Its cavity is much distended with soft, dark-red, postmortem blood clots, and the wall measures 2 mm. in its greatest thickness. The foramen ovale is patent, funnel-shaped, the apex leading into the left auricle, and measures 5 mm. in diameter. The right ventricle shows marked hypertrophy, being larger than the left ventricle, as is shown by the following measurements:

	Right, Cm.	Left, Cm.
Longitudinal	8	10
Transverse	7	3
Anteroposterior	8	6

The right ventricle has a separate apex which extends 1 cm. below the apex of the left ventricle. There is a slight transverse finger-like depression along its anterior surface, 4 cm. below the atrioventricular septum. Its wall measures 7 mm. in thickness. The tricuspid orifice is somewhat dilated, measuring 9.6 cm. in circumference. Its valves are diffusely thickened and present on their auricular surfaces, 5 mm. from their free margins, three firm, pyramidal, pearly-white masses, the largest measuring 3 mm. at its base and 5 mm. from base to apex.

The pulmonary artery is much enlarged, measuring 3 cm. in diameter. Its anterior wall is firm and bulging, whereas its posterior wall is soft and flabby. The pulmonary orifice is almost entirely obliterated, permitting only the passage of a small probe. On opening the orifice and artery the valves are found to be covered with numerous small, very friable, pendulous vegetations which entirely obliterate the sinuses behind the cusps. Beginning with the valves and extending along the inner, anterior surface of the pulmonary artery for an area 2 by 3 cm., is a friable, moderately firm, grayish-brown, pedunculated, wart-like outgrowth. This outgrowth fills the lumen of the pulmonary artery from valves to bifurcation, except for a small canalicular passage along the posterior wall. Section throughout the mass reveals a surface grayish-white and semitranslucent, mottled with small grayish-yellow areas of pultaceous material.

The left auricle is apparently of normal size. The left ventricular wall is firmly contracted, being beefy-red in color, and measuring 8 mm. in thickness. The mitral valves are diffusely thickened and present pyramidal masses similar to those on the tricuspid valves. The mitral orifice measures 8 cm. in circumference. The aortic valves show a moderate amount of diffuse thickening, with slight intervalvular adhesions. The aortic orifice measures 4 cm. in circumference.

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20. The necropsy was conducted by the Pathological Staff of the University of Louisville Medical Department.

Lungs: Dense, firm, fibrous adhesions anchor both organs to the chest walls. The right lung shows a cavity 2 by 1 cm., 2 cm. below the apex, containing grayish-yellow caseous material. Otherwise the lungs show nothing more than chronic passive congestion. Spleen: This is enlarged, measuring 17 by 9 by 4 cm.

Liver: This is firm, with edges somewhat rounded, surface brownish-yellow and finely nodular; cuts with increased resistance, cut surface presenting so-called nutmeg appearance. The ureter and pelvis of right kidney are distended with straw-colored fluid intermingled with brick-red, sand-like granules. This distention is due to the obstructing influence of the sand-like deposit in the distal portions of the ureter. The aorta is negative.

Microscopic Report.—Heart and Pulmonary Artery: Section made through the anterior wall of the pulmonary artery and attached vegetation shows fibrous thickening and moderate vascularity of adventitia, with numerous focal areas of leukocyte infiltration, chiefly of lymphocytes and plasma cells. The adjoining media exists as a narrow band adjacent to the adventitia, infiltrated with leukocytes, chiefly lymphocytes and plasma cells and focal collections of polymorphonuclear leukocytes; whereas the remaining portion of the media and intima are replaced entirely by products of inflammatory reaction, consisting of areas of frank purulent material, separated by an enormous amount of fibrin, red blood cells, and an occasional polymorphonuclear leukocyte. Within this inflammatory mass can be seen many intracellular and extracellular diplococci, of which a few are lancet-shaped.

Section through the pulmonary valve and adjacent wall of the artery shows proximally one-fourth of the valve to be markedly thickened, with dense, moderately cellular connective tissue, including many blood capillaries and spaces. Its concave surface is irregular and presents finger-like projections of connective tissue; whereas its convex surface is moderately smooth and irregular. The distal three-fourths of this valve is likewise thickened, with dense connective tissue, including numerous capillaries, and infiltrated with plasma cells. Both surfaces are irregular, showing projecting masses of fibrin, red blood cells and leukocytes, chiefly polymorphonuclear. The angle between artery and cusp is filled with a like inflammatory exudate.

Section through the pyramidal outgrowth of the tricuspid valves shows a central core of loosely arranged connective tissue, embracing capillaries and blood spaces and surrounded by a band of moderately dense connective tissue of varying thickness, infiltrated with an occasional lymphocyte. Overlying this dense band is the outermost lining of a single layer of endothelial cells.

Smears made from the cavity of the right lung show tubercle bacilli. Section through the apex of the right lung shows conglomerate tubercles. The liver shows sclerosis.

DISCUSSION

The heart, from a pathologic point of view, showed acute vegetations of pneumococcic origin, springing from the pulmonary valves and continuous with those that project from the wall of the pulmonary artery. The vegetations were so extensive that the lumen of the pulmonary artery was almost entirely obliterated. Aside from the acute reaction, the pulmonary valves showed diffuse and nodular types of sclerosis. The remaining valves likewise showed a diffuse sclerosis, whereas the tricuspid and mitral valves bore in addition the nodular type. The tricuspid orifice was somewhat dilated. The foramen ovale was patent. The right auricle and ventricle, especially the former, was markedly hypertrophied and dilated, whereas the left auricle and ven-

tricle were apparently of normal size. The aorta was entirely negative. The liver presented a typical picture of the so-called chronic passive congestion. The lungs showed tuberculosis.

With the heart findings the question of utmost importance is whether the diffuse sclerosis of the heart valves was one of congenital or acquired origin, and if so, was there present prior to the pneumonic attack, a pulmonary stenosis? From the clinical findings, namely, clubbing of the fingers, bulging of the chest, slow mental development, cyanosis, etc., as manifested when the patient first came under our observation, and from the pathologic picture of the heart at necropsy, we were no doubt dealing with a process of diffuse sclerosis and pulmonary stenosis, the origin of which dates from the fetal state. A compensatory alteration, which was present in the heart and which is commonly held to indicate a congenital origin of stenosis of the pulmonary valves, is patulousness of the foramen ovale. An open foramen ovale alone does not indicate with certainty, in doubtful cases of pulmonary stenosis, that it is of congenital origin, but its patency, linked with other findings noted in the foregoing, substantiates our claim in assuming the congenital origin of the affection. Having then an obstruction and leak from earliest infancy in the pulmonary orifice, the physiologic pathology would be a lowering of the diastolic pressure with a subsequent increase of the pulse pressure in the pulmonary artery, accompanied by a greater systolic output from the right ventricle in order to compensate for the leak. When the strain is compensated, we have hypertrophy of the right ventricle, but when the strain becomes too great, dilatation follows. As a result of dilatation, functional insufficiency of the tricuspid valves sets in, thus throwing a tremendous load on the right auricle, which in turn hypertrophies and dilates, with final engorgement of the venous vessels of the neck and liver, causing, therefore, in the liver, passive congestion and ultimately sclerosis.

The enormously enlarged right auricle accounts for the clinical finding of a pulsating mass in the suprasternal notch. The presence of a pulsation, thrill and bruit in the auricle synchronous with ventricular systole, constituted, no doubt, the clinical manifestations of either a dilated tricuspid orifice, or incompetent tricuspid valves. The apparent diastolic shock, so often encountered in aneurisms, can be accounted for by the rapid emptying of venous blood from the right auricle through the tricuspid orifice and patent foramen ovale.

The question now arises, if blood escaped through the foramen during diastole, why was there not present at necropsy hypertrophy and dilatation of the left auricle? This can be answered by saying that pulmonary stenosis prevented the normal allowance of blood from passing through the pulmonary system. As a result, the pul-

monary veins would likewise expel a relatively diminished quantity into the left auricle. In the case herein reported, the additional amount of blood received through the patent foramen ovale apparently adequately supplied the normal volume of blood, as was shown by the finding at necropsy of a normal sized left auricle and ventricle, and by the clinical manifestation of a radial pulse of good volume. If this were not true, that is to say, if normal equilibrium was not established, one would expect, on the one hand, a left auricle and ventricle reduced in size, together with a small radial pulse, or, on the other, hypertrophy and dilatation of the left auricle and ventricle with a strong radial pulse.

The murmurs heard previous to the pneumonic attack, synchronous with systole and diastole over the pulmonic area, were the clinical manifestations of pulmonary stenosis. It is denied by a number of writers, however, that a diastolic murmur is ever manifested in pulmonary stenosis, unless there is present an acute ulcerative condition. Nevertheless, Cantley[21] is of the opinion that a regurgitant murmur is present in most cases of pulmonary stenosis. He cites the case of a girl of 15 in whom there was present a double murmur in the pulmonic area. Several months later the patient developed rheumatic arthritis and died. Necropsy confirmed his statement. The pulmonary valves were found to be thickened and bore several acute vegetations.

Acute ulcerative involvement of a previously stenosed pulmonary orifice in most instances accentuates the pre-existent murmurs, especially the ones occurring synchronously with diastole. This clinical fact does not hold true in the case herein reported, for the reason that the enormous vegetation in the pulmonary artery almost entirely obliterated its lumen, thus producing a degree of obstruction in no wise inferior to that of the original stenosis.

As to what part the patent foramen ovale shared in the production of the murmurs heard, is a problem that we are unable to solve. If the patency produced murmurs, they must have been muffled by those resulting from the lesions of the pulmonary and tricuspid valves. It is possible that the diastolic murmur heard over the pulsating mass in the neck is in part a manifestation of this patency.

Tuberculous involvement of the lungs is quite common in all forms of pulmonary incompetency, and not infrequently is the terminal condition.

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21. Cantley, Ed.: A Case of Pulmonary Regurgitation, Lancet, London, 1902, **1**, 221.

PROGRESS IN PEDIATRICS

REVIEW OF THE LITERATURE OF THE PAST FIVE YEARS ON GONOCOCCUS VULVOVAGINITIS IN CHILDHOOD *

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This review comprises the most important articles on vulvovaginitis in children which have appeared during the past five years, with the exception of a few in foreign magazines to which we did not have access. Articles which consisted merely of a general description of the disease without any original observations were, as a rule, not included. A complete review of the literature from 1883 to 1912, by Generisch,[1] may be found in the Budapest *Medical-Surgical Presse* for 1911 and 1912.

CONTAGIOUSNESS

The extreme contagiousness of gonococcus infection among girls under puberty is universally admitted. As Meister[2] says, only a primary case is necessary in an institution; a little carelessness will do the rest, and when an epidemic has begun, only the strictest hygiene will prevent its rapid spread.

Hess[3] believes that it should not be regarded especially as an institutional disease, however, as it may be found in a considerable proportion of infants who live in crowded tenements in cities. Smith[4] notes that gonococcus vaginitis is confined largely to hospital practice, which would at once suggest that it is dependent, in part, at least, on poor social conditions. He also calls attention to the frequency with which feebleminded children act as centers of infection. This fact is an additional argument for their isolation, as such children are usually irresponsible in sexual matters.

Several factors are involved in this peculiar susceptibility of girls to gonococcus infection. Inclan[5] and Marshall[6] assert that the vaginal

* Submitted for publication Jan. 30, 1917.

1. Generisch, G.: Pest. Med.-Chir. Presse, Budapest, 1911, **47,** 405; 1912, **48,** 2.
2. Meister, W. B.: Am. Jour. Obst., 1910, **61,** 540.
3. Hess, A. F.: AM. JOUR. DIS. CHILD., 1916, **12,** 466.
4. Smith, R. M.: AM. JOUR. DIS. CHILD., 1913, **6,** 355.
5. Inclan, C.: Crón med.-quir. de la Habana, 1911, **38,** 422.
6. Marshall, C. F.: Brit. Jour. Child. Dis., 1910, **7,** 385.

mucosa of small girls is especially susceptible to gonococcus infection, whereas in women the uterus and adnexa are more vulnerable than the vaginal mucosa. Maier[7] and Taussig[8] say that this susceptibility to invasion by the gonococcus is largely contributed to by the fact that the pavement epithelium of the vagina in early life is soft and tender and in reality more closely resembles the columnar than the pavement type.

An additional and important factor, noted by Taussig,[8] is the condition of the labia in early life. Not only are they devoid of the protective hair, but also are somewhat everted. With the increase in the size of the labia after puberty, and above all, with the development of hair, the vestibulum is shielded. Beyond the age of puberty no cases of vulvovaginitis have come to Taussig's clinic concerning whom there was any suspicion that infection had occurred other than by sexual contact. On the other hand, the great majority of infections under puberty are accidental and nonvenereal. Several authors note the frequency with which gonococcus vaginitis follows measles and scarlet fever. Louis Fischer[9] states that at times as many as 10 per cent. of the scarlet fever patients at the Willard Parker Hospital have this sequel or complication. Adkins[10] advances the theory that the desquamative changes which follow scarlet fever prepare the ground for infection with the gonococcus.

FREQUENCY AND INCREASE

Jeans[11] found that 5.3 per cent. of 262 girls over 1 year of age who applied for treatment of various maladies at the Children's Hospital, St. Louis, over a period of five months, were suffering from gonococcus vaginitis in various stages of the disease. Of 149 physicians replying to the questionnaire of the American Pediatric Society's committee on vaginitis,[12] less than 2 per cent. had observed any decrease in the number of cases seen during recent years, while from 13 to 28 per cent. had noted an increase both in private and hospital practice. Koplik[9] is authority for the statement that the disease is not as prevalent abroad as in this country, but ventures no explanation.

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7. Maier, F. H.: Therap. Gaz., 1910, Series 3, **26,** 540.
8. Taussig, F. J.: Am. Jour. Med. Sc., 1914, **148,** 480.
9. Discussion of Barnett's Paper: Trans. New York Acad. Med., Sec. on Pediat., Am. Jour. Obst., 1913, **68,** 600.
10. Adkins, W. N.: Atlanta Jour. Rec. Med., 1913, **60,** 267.
11. Jeans, P. C.: Quoted by Taussig; see footnote 8.
12. Fife, C. A., Gittings, J. C., and Carpenter, H. C.: Trans. Am. Pediat. Soc., 1915, **27,** 331.

ETIOLOGY

Smith[4] and Barnett[13] investigated the source of infection in forty-six and thirty cases, respectively, with the following results:

	Cases
Hospitals or other institutions	19
Playmates	4
Other members of the family affected, especially mother or sister	26
Assault	4
Undetermined	23

Spaulding[14] also investigated the source of infection in seventy-five patients treated at the vaginitis clinic at the Children's Hospital in Boston, but apparently includes a number of cases in which the diagnosis was not clearly established by bacteriologic methods.

In the report of the committee on vaginitis of the American Pediatric Society[12] appear the following estimates of physicians as to the probable source of infection in private practice. The figures indicate the number of times each cause was mentioned:

	Cases
Indirect contact with adult members of the household, probably not immoral	69
The toilet seat, or toilet articles (in 12 instances, the school toilet was specified)	53
Nurse or attendant	28
Direct transmission	8
Playmates	5
Clothing	5
Diapers or dressings	4

In the same report we find the results of the observations of social workers and visiting nurses among dispensary and hospital patients. Infection can be traced to:

	Cases
Other members of family	102
Hospital wards	107
Hospital dispensaries	1
Playmates	31
Sleeping arrangements	14
Toilet and bathing facilities	10
Public schools	8
Temporary institutions	13
Permanent institutions	1
Day Nurseries	5
Bad habits or character	15
Rape	8
Doubtful	93

13. Barnett, N.: Arch. Pediat., 1913, **30,** 650.
14. Spaulding, Edith: AM. JOUR. DIS. CHILD., 1913, **5,** 248.

In Taussig's[8] report of sixty-six cases, the mother was found to be infected in only two instances. He is inclined to suspect other girls and toilet seats much more frequently than the mother. While admitting that infected towels or clothes may play an etiologic rôle, he points out that the gonococcus quickly loses its virulence when dried, which fact would usually render such articles innocuous. Forty-seven of his sixty-six patients were of school age. This probably influences his conclusions.

Generisch[1] emphasizes the German idea that gonococcus vaginitis in girls owes its origin in some cases to the superstition that a man can be cured of gonorrhea by infecting a virgin.

Mitchell and Quinn[15] report an unusual instance of epididymo-orchitis in a boy of 6 months which caused a small epidemic of vaginitis in four girl patients in the same ward.

BACTERIOLOGY

Louise Pearce[16] states that although it is generally admitted that, both morphologically and by culture, different strains of gonococci seem to be identical, the use of the complement fixation tests shows differences in the power of various strains of gonococci to bind complement when monovalent antigens are used. In her studies she used freshly isolated strains of gonococci with one exception—a gonococcus under cultivation for seven years. Nine were so-called adult strains and six were infant strains. The latter were recovered from patients with vulvovaginitis under 5 years. There were also three strains isolated from cases of ophthalmia. Her conclusions were as follows:

1. Two principal types of gonococci may be recognized by suitable immunologic tests; for example, agglutination and complement fixation. These two types correspond to the adult and infant types of infection with the gonococcus, seen clinically.

2. On the basis of these immunologic reactions the strains of gonococci isolated from three cases of ophthalmia are classed with the adult type.

3. A polyvalent antigen for the serologic diagnosis of a gonococcus infection should represent strains of the infant type of organism in order that both types of infection, infant as well as adult, may be recognized.

In the discussion of her paper Pearce emphasizes the fact that these types are not absolutely clear cut and distinct, but that it is highly probable that gradations between the two types exist; that the gonococcus may be a more or less labile group within itself; and that if a large enough number of strains were tested by their immunologic reactions, certain of these would be found partaking of the characteristics of both types. This experimental evidence seems to corroborate

15. Mitchell, A. G., and Quinn, N.: Arch. Pediat., 1915, **32,** 846.
16. Pearce, Louise: Jour. Exper. Med., 1915, **21,** 289.

the well recognized clinical difference between gonococcal infection as it occurs in infants and in adults.

Meister[2] insists that failure to find the gonococcus in the vaginal discharge in a suspicious case means no more than failure to find the tubercle bacillus in the sputum of patients with tuberculosis. In cases in which the organism cannot be demonstrated, he recommends the application of a strong solution of silver nitrate to the vaginal mucosa, although the gonococcus should be cultured when possible. Norris[17] also uses a 5 per cent. to 10 per cent. silver solution in such cases, applied the day before the smears are to be made.

R. M. Smith[4] believes that cultures are required to establish the positive diagnosis of gonococcal vaginitis, although the presence of the typical organism in the smear, he admits, is the usual criterion.

G. G. Smith[18] believes that the examination of smears often gives inconclusive evidence. In many instances the gonococcus is undemonstrable, especially in chronic cases, and even if gram-negative diplococci are seen within the pus cells, their identity is not always certain. Even when there is no discharge and the smears are negative, the so-called negative phase or latent period, the discharge is prone to reappear. Martha Wollstein[9] also occasionally encounters patients admitted to hospitals during this latent period.

Norris[17] admits the difficulty of demonstrating the gonococcus in the chronic cases, and believes therefore that all suspicious inflammation of the vulvovaginal region during infancy and childhood should be treated as specific (gonococcal). Furthermore, he believes that the gonococcus is readily isolated during the acute stage of the disease.

Spaulding[14] concludes that all cases of vaginitis with a persistent discharge which at any time has been profuse, are due primarily to the gonococcus. She found that in some cases smears were positive for many months after the discharge had stopped, especially in those which had received treatment, whereas in others a positive smear was difficult to obtain even during the acute stage.

Hess[3] believes that when bacteria cannot be demonstrated, if numerous pus cells are found in smears taken from the cervix, the infective organism is the gonococcus in the overwhelming majority of cases.

In the report of the American Pediatric Society[12] the summary of the opinion of thirty-seven bacteriologists is of interest. Approximately one third believe that identification is possible by observation of the morphologic and staining characteristics of the organism and by observation of its relation to other structures in the smear prepara-

17. Norris, C. C.: Jour. Am. Med. Assn., 1915, **65,** 327.
18. Smith, G. G.: Am. Jour. Dis. Child., 1913, **5,** 313.

tions; that is, by the fact that the gonococcus is an intracellular, gram-negative biscuit-shaped diplococcus. However, one half are of the opinion that the diagnosis may be safely made when such organisms predominate; when they are found in a profuse discharge from a situation susceptible of infection with the gonococcus; and when pus cells are present in proper position to the bacteria, especially when they show an increase of acidophilic granules. Three fourths of the bacteriologists believe that the percentage of error in this method of examination is very small. About one-third require typical cultural reactions in addition to these morphologic characteristics in order to fix the identity of the organism; one half of these advocates of the cultural method of differentiation demand it, regardless of the clinical history and physical signs, or of the evidence gained from coverslip preparations.

The cultural characteristics most commonly insisted on are: The organism should not grow on ordinary mediums, but readily develop on ascitic, hydrocele or blood agar at body temperature, with the formation in ascitic agar of moist, tiny, transparent, drop-like colonies of gram-negative diplococci of short longevity. These colonies should have thin, irregular, elevated edges and a crumb-like appearance on the center of growth. The culture must ferment dextrose, but no other forms of sugar. The pure culture does not affect ordinary test animals.

The technic of obtaining material for the smears is a matter of great importance. Barnett,[18] for example, found that smears taken from the fornix might be positive, whereas smears taken from near the hymen were negative. Willcox[9] prefers that smears be taken from the vault of the vagina and cervix, and Martha Wollstein[9] asserts that only by observing care to secure material from the inside of the vagina can extraneous contamination be avoided.

Van Gieson[19] states that the real value of the detection of the gonococcus is found at the very beginning and in the declining stages of the discharge. The intact leukocytic cell body is a sine qua non in diagnosis. Van Gieson finds that the cotton swab ordinarily used in making smears distorts the leukocyte and may injure the mucous membrane. Therefore he advocates the use of a medicine dropper and a 1 : 5,000 solution of mercuric chlorid in securing specimens for examination. The solution is injected into the vagina and drawn back into the dropper several times. It is then centrifuged and the sediment examined for cells and organisms. By a contrasting table he shows the efficacy of this method as compared with the usual moist or dry swab.

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19. Van Gieson, I.: Med. Rec., New York, 1910, **77**, 1001.

Norris[17] and Adkins[10] advocate this method of Van Gieson's. G. G. Smith[20] and Spaulding[14] prefer the use of the platinum loop.

Sinclair,[21] following the method of Rubin and Leopold,[22] used the electrically lighted female urethroscope in the diagnosis of gonococcus vaginitis in eighty-three infants. Smears were made through the urethroscope, from the cervix and vaginal mucosa. The platinum loop gave the best results, the moist swab was less satisfactory and the dry swab was much inferior. Van Gieson's irrigation method did not give as reliable results as the use of the urethroscope. Among the eighty-three cases, sixteen were found to be infected or highly suspicious on admission. Of the sixteen cases, 21 per cent. would have escaped detection without the use of the urethroscope, and only 30 per cent. showed any visible signs of discharge. The characteristic tendency of the disease to assume periods of latency is misleading.

Barnett[13] used a Skene urethral speculum and head mirror, as suggested by Koplik in 1893, in the diagnosis of vulvovaginitis, but later the Kelly electrically lighted endoscope was used. He also prefers the platinum loop for obtaining material for smears from the walls and floors of the vagina.

COMPLEMENT-FIXATION TEST

G. G. Smith,[18] in 1913, described the complement-fixation test as a serum reaction highly specific for gonorrhea. It is similar to the Wassermann reaction in syphilis. In a study of twenty-five cases, Smith found a positive complement fixation in eleven of twelve clinically positive cases, and in four cases in which the clinical evidence was inconclusive. In two of these four cases there had been no discharge for one and two years and smears were negative. The test was negative in three cases in which other evidences of cure were insufficient, but in seven others the clinical findings were corroborative. A year later Smith[20] published a further report on sixteen of these cases. Of nine, in whom there had been no recurrences and who gave negative complement-fixation tests in 1913, all but three gave weekly positive or suspicious reactions in 1914. This he explains by the greater sensitiveness of the tests which has developed from further use. Of seven patients who gave positive tests a year before, five were clinically well and two showed some discharge in which the gonococcus could not be demonstrated. Of the five which were apparently cured, two showed a weakly positive complement fixation; one a moderately positive reaction and two were negative. So strong is Smith's belief in the com-

20. Smith, G. G.: Am. Jour. Dis. Child., 1914, **7**, 230.
21. Sinclair, J. F.: Arch. Pediat., 1914, **31**, 29.
22. Rubin, I. C., and Leopold, J. S.: Am. Jour. Dis. Child., 1913, **5**, 58.

plement-fixation test that he interprets an absolutely negative result as proof of the absence of gonococcus infection.

Other authors are less didactic. Norris[17] believes that complement fixation and cutaneous tests are diagnostic if positive and carried out by an expert bacteriologist. Negative tests, however, do not rule out gonorrheal infection. Barney[23] looks on a moderately or strongly positive complement fixation as confirmatory proof in doubtful cases, and R. M. Smith[4] also considers it as a valuable aid in diagnosis. Kolmer[21] found only 50 per cent. of positive results in ten of Sinclair's cases, in which the diagnosis had been made with the aid of the urethroscope.

That the apparent vagaries in the results of complement-fixation tests may depend on the degree of involvement can be seen from the following:

Thomas, Ivy and Birdsall,[24] using specific and nonspecific antigens, failed to find a positive gonococcus complement fixation in adults when the vagina alone was involved. Williams[25] also states that gonococcus infection must reach at least the level of the uterus before a positive reaction occurs. Most of his patients were adults.

Schwartz and McNeill[26] also find that in adults the infection must involve the cervix before complement fixation is positive. In ten patients under 5 years of age the complement-fixation test was negative.

McNeill,[27] in another communication, reports the result of complement-fixation tests in eight children who had had gonococcus vaginitis from one to three years. Six had no discharge at the time the tests were made. Five gave a four plus positive reaction; two a double plus and only one a one plus. These results, few as they are, nevertheless show that infantile vulvovaginitis may be more than a local infection and that the general infection may be active after all local manifestations have disappeared. In acute cases when the complement-fixation test is negative, antigens may be prepared from pure cultures of the suspected organism and tested against a known antigonococcus serum.

Irons and Nicoll[28] obtained a positive complement fixation in seven cases of gonococcus vaginitis and negative results in five cases. In another series of five cases in which the gonococcus was obtained by culture, four showed a positive complement fixation. They investigated

23. Barney, J. D.: Boston Med. and Surg. Jour., 1916, **174,** 740.
24. Thomas, B. A., Ivy, R. H., and Birdsall, J. C.: Surgery, Gynec. and Obst., 1914, **19,** 390.
25. Williams, W. W.: Interstate Med. Jour., 1914, **21,** 1198.
26. Schwartz, H. J., and McNeill, A.: Am. Jour. Med. Sc., 1912, **144,** 815.
27. McNeill, A.: Arch. Pediat., 1913, **30,** 657.
28. Irons, E. E., and Nicoll, H. K.: Jour. Infect. Dis., 1915, **16,** 303.

a third series of seventeen patients who were suffering from scarlatina or diphtheria. All of these showed typical gonococci in smears, and some were also proved by cultural methods. Five of these seventeen cases gave a positive complement fixation, ten were negative and two were weak or doubtful. In one case with a purulent discharge in which no gonococci could be demonstrated, a positive complement fixation was obtained. In two cases in which a colon bacillus and a diphtheroid organism were found, the complement-fixation test was negative. They consider that, as a means of detection of gonococcus vaginitis, the complement-fixation test has a limited value. Positive reaction cannot be expected in early infection, and probably not even in cases of long standing, unless there is deep involvement. A negative reaction, therefore, is inconclusive.

The majority of bacteriologists who replied to the questionnaire of the American Pediatric Society[12] consider that the complement-fixation test is of decided value: when it is performed by a skilled serologist with satisfactory antigen and adequate controls; when the infection involves the deeper structures, and when it has been of duration long enough to cause the production of specific amboceptors.

PATHOLOGY

Sinclair[21] and Barnett[13] describe the lesions of vulvovaginitis found on a vaginal examination with the urethroscope. In most cases a small amount of dried pus was found on the labia, and pus was seen coming from the vagina, but the external appearance of the hymen might be normal in a pronounced gonorrheal process. The vagina was a dull pink color, with pus in the rugae and, occasionally, hemorrhagic spots. The cervix showed marked changes, being deeply congested, with pus exuding from the cervical canal. Superficial ulceration of the cervix was occasionally observed. In 30 per cent. of Barnett's fifty cases ardor urinae was present.

Hess[3] states that postmortem examinations show that in the subacute and chronic cases of vaginitis in infants the cervix is most frequently involved, and that the vagina generally shows no signs of inflammation. Cervicitis would therefore seem to be a more correct term than vaginitis. Kenessey[29] performed complete necropsies on two children who had gonococcus vaginitis and had died of pneumonia following varicella. In both cases a gram-negative intracellular diplococcus was found in the material within the uterus, and in the second case this organism was isolated in hydrocele agar. From the pathologic findings in these cases he concludes that the gonococcus in childhood

29. Kenessey, A.: Pest. Med.-Chir. Presse, Budapest, 1913, **49**, 360.

can invade not only the uterine cavity, but also the tubes and ovaries. Further, that the adnexa can be so severely involved as to cause irreparable damage to their later function.

COMPLICATIONS

Meister[2] finds that in infants suffering from gonococcus vaginitis complications are usually few and not serious — such as local dermatitis and enlargement of the inguinal glands. In older girls, on the other hand, any of the complications common to gonococcus infection in the adult may occur, including endometritis, salpingitis, peritonitis and, occasionally, endocarditis and pericarditis and arthritis. With this opinion the majority of observers seem to be in accord.

Perrin[30] believes that the rudimentary stage of development of the uterus and tubes in little girls explains the rarity of their involvement. Barney,[23] noting that the Bartholin and the Skene glands are undeveloped in childhood, as well as the uterus and tubes, ascribes to this fact that blood-borne metastases are rarely seen. Without specifications as to the age of the children, Marshall[6] and Spaulding[14] believe that gonococcus vaginitis, however contracted, may be followed by the same complications as in adult life.

Danger of infection of the eye seems to be much greater in early life than in adult life. Adkins,[10] who has never encountered a case of gonococcus arthritis, has seen quite a few infections of the eye complicating vaginitis. Van Gieson[19] also considers ophthalmia a serious danger.

Chapin's[9] experience has been more fortunate. He has rarely seen infection of the eye, and only one instance of tubal involvement. To offset this we have the following:

Marfan and Debre[31] report in extenso the case of a girl, aged 10½ years, suffering with chronic gonococcal vulvovaginitis, who developed symptoms of pelvic peritonitis and, afterward, endo-pericarditis and pleurisy. The most interesting fact was the recovery from the blood, by culture, of the gonococcus.

Schwers[32] records the case of a child 2½ years old in whom tenosynovitis of both arms, spondylitis and arthritis of the right sternoclavicular articulation and a polymorphous eruption were observed in the course of an acute attack of vulvovaginitis. Recovery ensued without treatment.

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30. Perrin, T.: Allg. med. Centr.-Ztg., 1910, **79,** 773.

31. Marfan, A. B., and Debre, R.: Bull. et mém. Soc. méd. d. hôp. de Paris, 1910, Series 3, **29,** 712.

32. Schwers, H.: Arch. de méd. d'enfants, 1914, **17,** 355.

Koplik[9] has known of four instances of fatal gonococcic peritonitis in the course of vaginitis occurring in patients at the Mt. Sinai Hospital, New York City.

Thirty-nine per cent. of the physicians who answered the questionnaire of the American Pediatric Society[12] have seen more or less severe systemic complications such as pus tubes, arthritis, pelvic or general peritonitis, septicemia, endocarditis, ophthalmia, etc., occurring in sixty or more cases.

We may sum up the actual proportion of complications to cases treated in the following reports of physicians who have made a special study of gonococcal vaginitis: Barnett,[13] 50 cases; Taussig,[8] 66 cases; Comby and Condat,[33] 18 cases; Sinclair,[21] 33 cases; Hamburger,[34] 21 cases; a total of 188 cases.

Complications	Number of Cases
Arthritis	3
General peritonitis	2
Pelvic peritonitis	2
Tubal infection	6
Ophthalmia	4
Periosteal disease of heel	1
Proctitis	3
Intense dermatitis of vulvae and thighs	2
Urethritis	1
Inguinal adenitis	1

Number of instances of complications, 25.
Percentage of cases showing complications, 13.3 per cent.

SEQUELAE

Whitehouse[35] suggests that some cases of endometritis, salpingitis and dysmenorrhea in the adult may be due to latent, uncured gonorrhea in childhood. Spaulding[14] has been unable to substantiate this, and Koplik[9] has had under observation several patients who had gonococcic vaginitis during childhood and who afterward married and were able to bear children. In the report of the American Pediatric Society[12] we find that only three of the gynecologists have treated adults who were known to have had gonococcus vaginitis during childhood. One has seen no sequelae, the other two have had to operate, one for pelvic peritonitis, and the other for peritonitis, salpingitis and oöphoritis. Although so few have seen instances in which vaginitis during childhood has manifested itself by sequelae in later life, 30 per cent. of the twenty gynecologists who expressed an opinion, positively state that gonococcus vaginitis of childhood may last after puberty; 40 per cent. more or less qualify their affirmative reply; the remaining 30 per cent. either definitely deny or gravely doubt its persistence.

33. Comby, J., and Mlle. Condat: Arch. de méd. d'enfants, 1914, **17,** 419.
34. Hamburger, R.: Deutsch. med. Wchenschr., 1914, **40,** 759.
35. Whitehouse: Practitioner, London, 1910, **84,** 485.

TREATMENT

Treatment of gonococcus vaginitis in children involves the use of local remedies and vaccines, and general constitutional measures. Most authors make use of some form of local treatment, some few believing that persistence in a reliable technic will result in cure, although admitting that much time and patience are requisite. Wolff[36] opposes local treatment in those past infancy on the score of its demoralizing influence. Rygier[37] enlarges on its difficulties and the lack of permanent results.

Adkins[10] believes that the disease runs its course in spite of all one can do to cure it. Certain local measures he finds of temporary benefit. Among these is the injection of suspensions of living lactic acid bacilli.

Whitehouse[35] also has treated eight patients with cultures of lactic acid bacilli without the use of other measures. He obtained cessation of discharge and disappearance of gonococci and septic organisms in from fourteen days to three weeks. He does not know whether or not these results are permanent, however.

Taussig[8] believes in rest and general tonic treatment. He does not believe in irrigations, but prefers instillations of a solution of argyrol, 25 per cent., in the early stages; later a 1 per cent. to 4 per cent. solution of nitrate of silver.

G. G. Smith[20] advocates mechanical cleanliness by means of irrigations with potassium permanganate, 1:4,000, and the prolonged use of silver salts, such as argyrol. He continues these treatments for one month after all discharge has disappeared.

Perrin[30] has treated over 100 cases during the last ten years with injections of protargol 5, water 8, glycerin, q. s. ad. 50. He claims that all were radically cured within fourteen to twenty days. Most of the cases were chronic and had received a variety of other forms of treatment.

The most elaborate technic is described by Norris[17] as follows: The child is put in the Sims or knee-chest position. The hymen usually must be sacrificed. The vagina is washed with weak potassium permanganate solution and swabbed with 25 per cent. argyrol solution. It is then thoroughly dried with strips of gauze, and the drying completed with an empty atomizer. The child is kept in the Sims position for twenty to thirty minues to allow air to enter the vagina. Finally the vagina is flooded with a weak solution of silver nitrate, gradually increased in strength, and glycerin added. The above treatment is carried out three times a week. In the interim the mother or nurse uses a weak permanganate or argyrol solution introduced with a soft

36. Wolff, M.: Chicago Med. Recorder, 1913, **35,** 462.
37. Rygier, S.: Deutsch. med. Wchnschr., 1911, **37,** 2334.

rubber ear syringe. By this method Norris cured fourteen patients in an average of twelve weeks, the longest time being eighteen weeks.

Willcox,[9] after trying all methods of treatment, believes that the disease is controlled but not cured. Fisher[9] has abandoned treatment other than the use of irrigations of magnesium, alum and water. He also advocates the use of general tonic treatment, namely, change of air, arsenic, cod liver oil and iron.

Rubin and Leopold[22] insist on the importance of determining the extent of the deep lesions before beginning treatment. For this purpose the electrically lighted female urethroscope should be employed. When irrigations are resorted to, the douche tip should enter the vagina for at least 1½ inches. Applications by swabs used without the urethroscope are injurious and useless. When strong silver solutions are applied to the cervix and vagina, it is well to keep the child in bed for a few days.

Barnett[13] also advocates the use of the electrically lighted urethroscope in treatment in order to apply the medicament directly to the cervix. This he considers important, as the involvement of the cervix is not easily amenable to the ordinary douche or irrigation. He prefers Lugol's solution 1 : 500. With the use of the urethroscope he obtains a cure in a month; whereas at the end of six months only seven of his twenty-six patients undergoing prolonged systematic treatment were cured by ordinary irrigations.

Freeman[9] states that local treatment should not be limited to one method, as a change often brings good results. He also believes in the use of the endoscope.

Kerley[9] sounds a timely warning that a large number of cases should be studied before reporting results from any form of treatment, as occasionally a run of mild infections occurs and the physician, in such an event, would become unjustifiably enthusiastic about his method of treatment.

VACCINE TREATMENT

One of the most ardent advocates of the use of vaccines is B. W. Hamilton,[38] who treated eighty-four patients with 90 per cent. of cures in an average time of fifty days. These figures he contrasts with 260 patients treated by irrigation alone, in whom there were 60 per cent. of cures in an average time of 300 days (ten months). He used two stock vaccines and one freshly prepared from an eighteen-hour blood agar culture taken from an adult male with urethritis. He describes at length his method of administering vaccines. Apparently, local treatment was not used.

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38. Hamilton, B. W.: Am. Jour. Obst., 1910, **61**, 837.

Wolff[36] believes that gonococcus vaginitis is one of the diseases in which vaccine treatment has proved itself to be especially advantageous if given in a careful and judicious way. Stock vaccines do not show a constant efficiency and have no scientific basis. Vaccines should be made from fresh cultures, and should include the organisms ordinarily found in conjunction with the gonococcus, namely, staphylococcus, diplococcus (not gonococcus) colon bacillus, pseudodiphtheria bacillus. Wolff treated with vaccine forty patients from 1 to 14 years of age, without local measures other than external cleanliness. Many of the cases were chronic. The number of injections varied from four to ten, with an average of seven, injections being given every five to seven days. After one year only one case is known to have relapsed. He believes autogenous vaccines to be 100 per cent. efficient.

Another strong advocate of vaccine treatment is W. J. Butler,[39] who has reported several series of cases treated with monovalent and polyvalent stock vaccines; the former he usually finds more efficacious. His results, without local treatment, show 75 to 85 per cent. of cures in from ten days to two months, in both acute and chronic cases. By cure he means the disappearance of discharge, and "several" negative smears. He finds the vaccine treatment incomparably more efficient than local treatment, and hopes that the latter will be abandoned except in rare instances.

Rygier[37] used a stock vaccine made from many strains of gonococci, and believes that vaccine treatment offers greater certainty and rapidity of cure than any other known method.

Comby and Condat[33] treated 18 patients with the vaccine of Nicolle. Marked improvement was noted after the second injection, but no data are given as to the subsequent course. They believe that the results from vaccine compare very favorably with those from local treatment, with the added advantage that local treatment is unnecessary except in unusually stubborn cases.

Spaulding[14] used autogenous vaccines in conjunction with various forms of local treatment. She believes that vaccines are not specific, but an added factor for good.

Whitehouse[35] noted disappearance of all symptoms in two cases after the fifth and sixth injections of vaccine, and Adkins[10] reports good results in a series of thirty-two cases.

Strassberg[40] believes in vaccine in the early stages, before many forms of local treatment have been used. Later he advocates both local and vaccine treatment.

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39. Butler, W. J.: Interstate Med. Jour., 1910, **17,** 510.
40. Strassberg, M.: Wien. klin. Wchnschr., 1914, **27,** 889.

Carrau[41] used the vaccine of Nicolle and Blaziot[42] in fifteen patients, five to twelve years of age, without any local treatment. In only two did the gonococcus disappear, although the discharge diminished markedly in all the others.

Cecil[43] used a sensitized vaccine, that is, a vaccine treated with specific homologous serum, with satisfactory results. Some of his patients were adults, however, so that the figures are not available as they apply to children.

Barnett[13] could find no improvement in the vaginal discharge in patients treated with vaccines, but the complication of arthritis yielded rapidly.

Tieche[44] notes the danger of "sexual trauma" from the use of local treatment, but concludes that the combination of vaccines and local measures offers the best hope for cure.

Boas and Wulff[45] treated twenty-six patients, two with vaccine alone, seven with vaccines and local measures, and seventeen received only local treatment. The best results were obtained with the combined treatment. The two patients treated by vaccine alone quite certainly showed no improvement.

The toxicity of gonococcal vaccines is considered an almost insurmountable obstacle by Murphy and Kreuscher,[46] although Nicolle and Blaizot[42] claim they have succeeded in entirely overcoming this toxicity and in rendering the vaccines stable.

Marfan and Debre[31] found Wright's vaccine inefficacious. Hamburger[34] has used stock vaccines in the treatment of twenty-one children. He fails to state his definite results, which evidently were unfavorable.

G. G. Smith[20] does not believe that results with vaccine are satisfactory in gonococcus infection of the mucous membranes either of the male or female.

Freeman[9] is inclined to believe that vaccines have done little if any good.

Kerley[9] used stock vaccines in thirty-six cases without any noteworthy results.

Wollstein[9] has used both autogenous and stock vaccines, according to the opsonic index. The results were not encouraging.

Of pediatricians who answered the questionnaire of the American Pediatric Society[12] as to the use of vaccines, twenty favored it and

41. Carrau, A.: Rev. med. d. Uruguay, Montevideo, 1915, **18,** 79.
42. Nicolle, C., and Blaizot: Jour. d'urol., 1913, **4,** 734.
43. Cecil, R. L.: Am. Jour. Obst., 1915, **72,** 528.
44. Tieche: Cor.-Bl. f. schweiz. Aerzte, 1912, **42,** 159.
45. Boas, H., and Wulff, O.: Hospitalstidende, 1910, 5 R., p. 801.
46. Murphy, John B., and Kreuscher, P. H.: Interstate Med. Jour., 1914, **21,** 1214.

eleven found no material benefit from it. Approximately two thirds of the bacteriologists throughout the country also favored its use. The majority favored the use of autogenous vaccines, or, in the event that such were not available, some sanctioned the use of polyvalent stock vaccines. About four fifths of the bacteriologists believe that, if vaccines are properly made and administered, they are free from danger. The remaining fifth deny that they are harmless.

OPSONIC INDEX

Hamilton[38] could find no relation between the opsonic index and the activity of the vaginal discharge, while using vaccine treatment.

Wolff[36] believes that the determination of the opsonic index is not essential if care is taken to regulate the dosage of vaccine by the reaction and the clinical needs of each individual case.

Butler[39] originally controlled the administration of vaccine by the determination of the opsonic index, but abandoned it after finding the proper dosage and interval. He advocates small doses, 5 to 50 million at first, repeated at five-day intervals.

The only reference found to the use of serum in the treatment of gonococcus vaginitis was that by Marfan and Debre,[31] who used antimeningococcic serum subcutaneously. Unusual and grave anaphylactic symptoms resulted.

DURATION AND LATENCY

The tendency toward chronicity of gonococcus vaginitis in children is one of its most noteworthy and generally admitted characteristics. As Adkins[10] says, a consideration of the well-known chronicity of the disease in adults would give sufficient grounds for a like expectation in children. The tendency toward latent periods followed by recurrences is more marked in children.

Barnett,[13] in studying fifty cases, found that the duration of the disease, according to the history, varied from one week to several years. One case had existed for six years, with gonococci present in the vaginal pus. The average duration was eight and one-half months. In twenty-six cases, Spaulding[14] found the average duration was twenty months. The disease, she believes, may extend over many years, during which time there may be many recurrences and the periods of latency may be as long as eighteen months.

Rubin and Leopold[22] believe that the cause of the chronicity of gonococcus vaginitis in children lies in the anatomic construction which does not permit of free drainage. This is not due to the hymen, but to the fact that each segment of the vagina serves as a valve to dam back the discharge, as the vaginal walls are constantly in close contact.

Then, too, the vaginal portion of the cervix shows the most marked changes, and, at the same time, is in the most disadvantageous position for drainage and treatment.

R. M. Smith[4] gives the following results in thirty cases: Cured, 8 (no symptoms for from three to twenty-four months); 4 negative complement-fixation tests; under treatment from one and one-half to twenty-one months; did not continue treatment, 14; still under treatment, 8 (from one month to two years).

Barnett[13] found that the discharge soon ceased with any method of treatment. This, however, did not constitute a cure, as smears may remain positive for months after all visible signs of discharge have ceased.

Kerley[9] notes that cases clear up spontaneously after an indefinite course, due to the attenuation of the organism. This explains the comparative rarity of a course extending beyond the third or fourth year.

Koplik[9] also believes that the disease is self-limited.

CURE

R. M. Smith[4] thinks that the disappearance of all symptoms, after adequate treatment, with persistent negative smears and negative complement fixation, is a fair indication of a cure. The reappearance of a discharge in such patients, when the original source of infection persists and there has been no reform in the habits of the patient, is more likely to be a reinfection than a relapse.

G. G. Smith[18] believes that when other signs point to a cure, the complement-fixation test should be used as a court of last appeal. If a case proves to be a cure, with a negative complement fixation, Smith also believes that a recurrence of discharge containing the gonococcus signifies a reinfection and not a relapse.

Spaulding[14] believes that the most efficient treatment does not insure a permanent cure. She found that twenty-four of twenty-six patients had a recurrence of the discharge after apparent cure, in from three weeks to six years. Apparently she does not consider the possibility of reinfection!

The criteria on which it is believed that a cure can be predicated may be summarized as follows:

Barnett[13] and Wolff[36] base a cure on three negative smears taken at weekly intervals after all treatment has been stopped.

Maier[7] demands an additional fourth smear after a three-weeks' interval — six weeks in all.

Hamilton[38] requires four negative smears at weekly intervals and two additional smears at two-week intervals, eight weeks in all.

Norris[17] bases a cure on three negative bacteriologic and physical examinations made at intervals of two weeks, the last examination being preceded by chemical irritation with a nitrate of silver solution.

PROPHYLAXIS

Smith[4] believes that we must recognize that we are dealing with a social evil, and that the medical treatment is only a part of what needs to be done in the attempt to eradicate the disease. Parents must be made to recognize the contagiousness of the disease if we are to utilize one of the most important factors in preventing its spread.

Hess[3] states that vulvovaginitis is another instance of the healthy but dangerous "carrier," which is emphasized by the difficulty in recognizing the latent cases. By means of a provocative inoculation of gonococcus vaccine he has been able to convert the concealed "carrier" into the "open" case, and in this way to discover many cases which had eluded detection. Furthermore, he believes that the inoculations have some prophylactic value, and that they either confer protection or render subsequent infection of a mild character, so that it assumes a bacteriologic rather than a clinical type.

Spaulding[14] believes that the physician should realize the importance and prevalence of the disease and institute stricter preventive measures, both in hospital and private practice.

Adkins[10] notes that the negro child nurses in the South commonly are infected with the gonococcus, and believes that there should be a law compelling nurses to undergo examination. He advocates the use of silver salts in the vagina immediately after birth, and believes that the vagina is even more liable to infection than the ocular mucosa.

Taussig[8] also advocates the prophylactic injection of a drop of 2 per cent. solution of silver nitrate into the vestibulum vaginae in all new-born infants, when there is any evidence of gonorrhea in the mother. He advocates making gonococcus infection reportable to the health authorities, the education of mothers, and most important of all, the adoption of the U-shaped toilet seat with the low bowl in all public lavatories, schools, tenements, play-grounds, etc.

Meister[2] also advocates the use of a 2 per cent. solution of silver nitrate in swabbing the labia and vagina of new-born girls, followed by an irrigation with a saturated solution of boric acid.

It is generally admitted that the routine examination of girls before admission to an institution should include determination of the presence or absence of gonococcal infection.

Willcox[9] states that at the Bellevue Hospital, New York, girls are kept in the detention ward for three days while smears are taken daily from the cervix and vaginal vault. Absence of pus cells and organisms must be shown before the child is admitted to the wards.

In an editorial in the *Lancet*[17] attention is called to the variable incubation period in true gonococcus vaginitis, which may be as long as three weeks. There is, therefore, constant danger of the introduction of the contagion into general wards even when a negative smear has been obtained on admission.

Butler[39] insists on isolation, especially because one attack does not confer immunity against reinfection. He also insists that the disease is acquired by infection of the genitals. The usual sources he believes to be the common bath tub, common toilet and the hands of the nurse. He does not believe that the laundry plays any part in epidemics.

G. G. Smith[20] advocates allowing children to go to school if the mother is warned not to let her child use the toilet.

Sinclair[21] believes that a campaign of education should be carried out, especially in the home and in all kinds of institutions dealing with the various phases of child welfare, such as day nurseries, asylums, hospitals, public bathhouses, recreation centers, schools, etc. He also advocates the systematic examination of all inmates of institutions, including lay helpers; the establishment of special clinics in hospitals; and that boards of health should be empowered to make gonorrhea a reportable disease. Barnett[13] also subscribes to most of these precautionary methods.

The opinion of physicians who replied to the questionnaire of the American Pediatric Society[12] as to the importance of various prophylactic measures is shown as follows:

	Points
1. Hospital care	88
Under this heading are included, isolation, prolonged treatment till cured, improved technic in handling and in treatment, special instruction to nurses, especially night nurses, etc.	
2. Instruction to the laity	52
Under this heading are included printed and verbal instructions as to the nature of the disease, danger of transmission, best means for prophylaxis, etc.	
3. Schools	20
Examination and exclusion of positive cases, care as to the toilets, etc	
4. Control by boards of health	16
Compulsory report of cases, compulsory treatment, etc.	
5. Physicians	15
Instruction as to the importance of early recognition, prolonged treatment, etc.	
6. Institutions and tenements	11
Adequate medical supervision, care as to toilets, etc.	
7. Medical-sociologic relief	7
Systematic sociologic study, follow-up nursing, etc.	

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47. Editorial: Lancet, London, 1910, **2**, 1354.

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